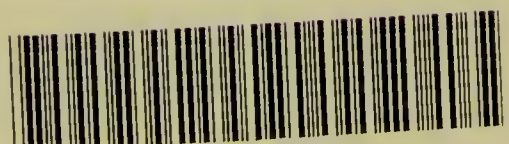

THROMB

EMBOL

Allbutt

Dr. Payne,
With kind regards of
W. H. Welch.

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THROMBOSIS

AND

EMBOLISM

BY

WM. H. WELCH, M.D.

Allbutt's

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DISEASES OF BLOOD-VESSELS

THROMBOSIS

Definition.—A thrombus is usually defined as a blood-coagulum, formed in the heart or vessels during life. This definition applies to most cases; but, in order to meet the objections of those who do not concede that all thrombi are genuine coagula, and to give due prominence to the participation of blood-platelets and corpuscles, a thrombus may be more broadly defined as a solid mass or plug formed in the living heart or vessels from constituents of the blood. Thrombosis is the act or process of formation of a thrombus, or the condition characterised by its presence.

Structure of thrombi.—The formed elements which may enter into the composition of fresh thrombi are blood-platelets, fibrin, leucocytes, and red corpuscles. These elements may be present in varying number, proportion, and arrangement, whence there results great diversity in the appearance and structure of different thrombi.

The two main anatomical groups of thrombi are the red and the white thrombi. Many of the mixed thrombi may be regarded as a variety of the white thrombus. In addition there are thrombi of relatively minor importance composed wholly or chiefly of leucocytes, of fibrillated fibrin or of hyaline material.

Red thrombi.—These are formed from stagnating blood, and in the recent state do not differ in appearance and structure from clots formed in shed blood. They are made up of fibrillated fibrin and of red and white corpuscles in the same proportions as in the circulating blood, or the white corpuscles may be somewhat in excess. If any part of such a red thrombus be exposed to circulating blood, white material, consisting of platelets with fibrin and leucocytes, is deposited upon it. This deposit may aid in distinguishing the thrombus from a post-mortem clot.

White and mixed thrombi.—Most thrombi are formed from the circulating blood, and are white, or of a mixed red and white colour. The white or gray colour is due to the presence of platelets, fibrin, and

leucocytes, occurring singly, or, more frequently, in combination. The admixture with red corpuscles is not an essential character of the thrombus, although it may be sufficient to give it a predominantly red colour.

Fresh white human thrombi, when examined microscopically, are seen to be composed of a granular material, usually in islands or strands of varying shape and size, around and between which are fibrin and leucocytes with a larger or smaller number of entangled red corpuscles. The granular matter, to which the older observers attached comparatively little importance, and which they interpreted as granular or molecular fibrin or the detritus of white corpuscles, is now known to be an essential constituent of the white thrombus, and is composed chiefly of altered blood-platelets. Intact polynuclear leucocytes are usually numerous in the margins of and between the masses of platelets, and may be scattered among the individual platelets. Not less important is the fibrillated fibrin, which is generally present in large amount. It is particularly dense in the borders of the platelet-masses, and stretches between them in anastomosing strands, or as a finer network containing red and white corpuscles. Within the accumulations of platelets in fresh thrombi fibrin is often absent, or is in small amount. These various constituents of the thrombus often present a definite architectural arrangement, and soon undergo metamorphoses which will be described subsequently.

Thrombi of the kind just described, and as we find them at autopsies on human beings, are completed products, and it is difficult, indeed generally impossible, from their examination to come to any conclusion as to the exact manner of their formation; particularly as regards the sequence and relative importance of their different constituents. So long as the knowledge of the structure of thrombi was limited to that derived from the study of these completed plugs, the coagulation of fibrin was generally believed to be the primary and essential step in their formation; although Virchow pointed out the greater richness in white corpuscles as a feature distinguishing them from post-mortem clots.

Zahn, in 1872, was the first to make a systematic experimental study, mainly in frogs, of the mode of formation of thrombi. He came to the conclusion that the process is initiated by the accumulation of white corpuscles which, by their disintegration, give rise to granular detritus. This is quickly followed by the appearance of fibrin, which was readily accounted for by Weigert on the basis of Alexander Schmidt's well-known suggestion of the origin of fibrin ferment from disintegrated leucocytes. Zahn's views, anticipated in part by Mantegazza in 1869, and confirmed by Pitres in 1876, gained prompt and wide acceptance.

Continued experimental study of the subject, however, especially upon mammals, led to opposition to Zahn's conclusions, and favoured the opinion, now generally accepted, that the ordinary white thrombus starts

as an accumulation not of leucocytes but of blood-platelets. The investigators chiefly concerned in the establishment of this doctrine are Osler (1881-82), Hayem (1882), Bizzozero (1882), Lubnitzky (1885), and Eberth and Schimmelbusch (1885-86).

There is no difficulty in producing thrombi experimentally by injury, either mechanical or chemical, to the vessel-wall; or by the introduction of foreign bodies into the circulation. If the early formation of such a thrombus be observed under the microscope in the living mesenteric vessels of a dog, as was done by Eberth and Schimmelbusch, it is seen that the first step consists in the accumulation of blood-platelets at the seat of injury. These plates, in consequence of their viscous metamorphosis, at once become adherent to each other and to the wall of the vessel, and thus form plugs which may be subsequently washed away into the circulation, but which sometimes so increase in size as to obstruct the lumen of the vessel completely. Red and white corpuscles may be included in the mass of platelets; but their presence at this stage is purely accidental; they are not to be regarded as essential constituents of the thrombus in its inception.

The microscopical examination of young experimental thrombi confirms the results of these direct observations, and affords information as to their further development. To obtain a clear idea of this development, thrombi should be examined at intervals of minutes from their beginning to those half an hour old or older. I reported the results of such an experimental study in 1887. The material composing the youngest thrombi formed from the circulating blood appears macroscopically as a soft, homogeneous, gray, translucent substance of viscid consistence. Microscopically it is made up chiefly of platelets, which are seen as pale, round, or somewhat irregular bodies, varying in size but averaging about one-quarter the diameter of a red corpuscle.

Leucocytes, which may be present in small number at the beginning, rapidly increase in number, and within the first fifteen minutes to half an hour they are usually in such abundance that at this stage of its formation they must be considered an essential constituent of the thrombus. They tend to collect at the margins of the platelet-masses and between them. These leucocytes are nearly all polynuclear, and usually present no evidence of necrosis or disintegration.

With the accumulation of leucocytes, fibrillated fibrin, which at first was absent, makes its appearance; being, as pointed out by Hanau, especially well marked and dense in the margins of the masses of platelets. Within these masses it is usually absent. The rapidity with which leucocytes and fibrin are added to the masses of platelets varies much in different cases. At the end of half an hour the thrombus may be composed of platelets, leucocytes, and fibrin with entangled red corpuscles, in essentially the same proportions and with the same arrangement as in the human thrombi already described; or even after several hours it may still consist almost wholly of platelets.

The prevailing view is that platelets exist in normal blood, where

they circulate with the red corpuscles in the axial current. In accordance with this view, many observers, following Eberth and Schimmelbusch, explain the beginning of a white thrombus by the accumulation of pre-existing platelets upon a foreign body, or, in consequence of slowing or other irregularities of the blood-flow, on the damaged inner wall of the heart or vessels. Contact with the abnormal surface sets up an immediate viscous metamorphosis of the platelets, whereby they adhere to each other and to the foreign body or vascular wall. Eberth and Schimmelbusch designate this process as conglutination, and distinguish it sharply from coagulation, which they regard as a later event in the development of the thrombus.

Those who hold with Löwit, that platelets do not exist in normal blood, believe that they are produced at the moment of formation of the thrombus, as the result of injury to the blood; and many who believe that they are in normal blood not as independent elements, but as derivatives from leucocytes or red corpuscles, consider it probable that those in the thrombus are formed, at least in part, in consequence of such injury. Although there are observations which suggest that platelets may be derived from leucocytes, there is no evidence that the masses of platelets found in incipient thrombi come from leucocytes previously attracted to the spot.

Strong evidence has been recently presented, by Arnold, F. Müller, and Determann, in favour of the origin of platelets from red corpuscles. Wlassow, working in Ziegler's laboratory, finds that the white thrombus is formed primarily by the destruction of red corpuscles, and is composed at the very beginning of shadows of red corpuscles, corpuscular fragments both with and without hæmoglobin, granular material and platelets of nucleo-proteid substance; all derived from disintegrating red corpuscles. A similar view is entertained by Mosso, Klebs, Arnold, Ziegler, and F. Müller.

The accumulation of leucocytes in the young thrombus may be explained partly by mechanical causes,—the most evident being the projecting, irregular, sticky substance of the platelet masses associated with slowing and eddies of the blood-stream,—and partly by chemiotactic influences.

Whatever difficulties there may be, in accounting for the fibrin, relate to the general subject of coagulation of the blood (see Professor Foster's article in vol. vi. p. 403) rather than to the special conditions of the thrombus. As to the participation of platelets in the production of fibrin, opinion is divided; and upon this point the study of thrombi has not afforded conclusive evidence one way or the other. The usual absence of fibrin within the platelet masses for a considerable time after their formation may be thought to speak against the generation of fibrin-ferment by the platelets. But if, as is probable, the platelets contain nucleo-proteid, it would be reasonable to suppose, in accordance with current physiological ideas, that they can yield one of the fibrin factors; and it may be that in these compact masses there is not

enough fibrinogen furnished by the plasma to generate an appreciable amount of fibrin. The characteristic dense ring of fibrin immediately around the platelet masses, where there is abundant fibrinogen, could be interpreted in favour of the liberation of fibrin-ferment by the collected platelets. By the time, however, that the fibrin appears, leucocytes have also accumulated in the same situation; and they, either alone or together with the platelets, may be the source of the ferment; although, as already stated, the leucocytes in young thrombi generally show apparently intact nuclei and cytoplasm.

Does the recognition of the described mode of development of a white thrombus necessitate a radical break, such as that made by Eberth and Schimmelbusch, with the old and still common conception that a thrombus is essentially a blood coagulum? This question applies only to the first stage of formation of a white thrombus, for the completed thrombus is undoubtedly a coagulum. It is, however, of both scientific and practical interest to inquire whether coagulative phenomena usher in the process of thrombosis or are merely secondary. A decisive answer to this question cannot be given until we are better informed than at present concerning the chemistry and morphology of coagulative processes, and the source and properties of the granular material constituting the youngest thrombi. The possibility that this material is already coagulated, and falls into the category of the coagulative necroses, has been suggested by Weigert; but without any proof of this view. There is greater probability that the accumulation and metamorphoses of the so-called platelets in beginning thrombi represent a preparation for coagulation or a first step in the process. As Hammersten has pointed out, two chemical phases are to be distinguished in the process of coagulation; namely, the formation of fibrin ferment from its zymogen, and the transformation of fibrinogen into fibrin under the influence of this ferment. Morphological phases may also be distinguished, and the platelet stage of thrombus formation may be interpreted as the first morphological phase of coagulation in circulating blood. According to Wlassow a similar morphological phase may be recognised in the clotting produced by whipping shed blood. It would lead too far afield to enter here into a discussion of the arguments in favour of this view; but much in its support is found in recent chemical and morphological studies of extravascular and intravascular coagulation, and of the anatomical and chemical characters of blood platelets.[1] It does not appear, therefore, that we are called upon at present to make any such radical revision of the traditional conception of white thrombi as coagula, as has been advocated of late years by some writers.

Leucocytic thrombi.—As has already been explained, leucocytes, although they do not usher in the process of ordinary thrombosis, make their appearance at an early stage, and often accumulate in such numbers as to constitute a large part of the thrombus. My studies of experi-

[1] This recent work has been critically reviewed by Löwit in Lubarsch-Ostertag's *Ergebnisse*, 1897.

mental and human thrombi have led me to assign to them a more important part in the construction of white thrombi than that indicated by Eberth and Schimmelbusch. Whether the regular mural white thrombi ever arise as a collection of leucocytes, in the manner described by Zahn, is uncertain. Such a mode of development, if it occurs, is, I think, exceptional. Intravascular plugs, however, occur, which are made up wholly or predominantly of polynuclear leucocytes. These are found mainly in small vessels in acutely inflamed regions, where they are to be regarded as inflammatory and probably chemiotactic in origin. Leucocytic masses may also be found after death in small vessels in leucocythæmia, and in diseases with marked leucocytosis; but it is probable that these are not genuine obstructing plugs.

Purely fibrinous thrombi.—As will be described subsequently, fibrin usually increases in amount with the age of the thrombus. The masses of platelets may be replaced by fibrin, and leucocytes may degenerate; so that many old, unorganised thrombi consist of practically nothing but dense fibrin, in places hyaline. I do not, however, desire now to call especial attention to these old, metamorphosed thrombi.

One sometimes finds in inflamed areas, less frequently under other circumstances, the vessels, particularly those of small size, partly or completely filled with fibrillated fibrin, presenting such an arrangement and configuration as to indicate coagulation during life. Neither leucocytes nor platelets need take part in the formation of these plugs of pure fibrin, although sometimes they are present. K. Zenker has well described the microscopical appearances in these cases. Whorls or brush-like clumps of fibrin may spring at intervals from the wall of the vessel, where they are attached especially to necrotic endothelium or to points devoid of endothelium. The fibrin may be disposed regularly, often in stellate figures, around definite centres in which, perhaps, a necrotic cell or fragment, endothelial or leucocytic, or a clump of platelets can be demonstrated. The fibrin is often notably coarse. The affected vessels are not usually filled completely with fibrin, and they can be artificially injected. In croupous pneumonia such fibrinous masses are regularly present, both in capillaries and larger vessels of the hepatised area. These purely fibrinous coagula are of anatomical rather than clinical interest.

Hyaline thrombi.—These are of more interest and importance than the purely fibrinous and leucocytic thrombi just described. The presence of hyaline material in old white thrombi will be spoken of subsequently. To von Recklinghausen we especially owe the recognition of hyaline thrombi as a distinct class. They are found especially in the capillaries, but may occur also in the smaller arteries and veins. The capillaries are filled with a refractive, homogeneous, translucent, colourless or faintly yellow material, which stains well with Weigert's fibrin dye. The same material may partly or completely fill the smaller arteries and veins. Balls, as well as cylindrical masses, of this hyaline substance may be found, especially in the cerebral vessels.

This hyaline thrombosis has been observed in a variety of conditions, partly general, partly local. It occurs especially in infective and toxic diseases. Kriege found extensive hyaline thrombosis in the small vessels after freezing the rabbit's ear. Von Recklinghausen had previously attributed to this cause spontaneous gangrene of both feet occurring in an old woman who had suffered repeatedly from slight frost-bites; and he likewise found the same hyaline vascular plugs in cases of mortification following experimental ergotism. Capillary hyaline thromboses are common in the lungs in pneumonia, and in hæmorrhagic infarcts. In general infective and toxic states they may be present in the liver, the lungs, and, above all, in the kidneys.

The most striking examples of this form of thrombosis, with which I am acquainted, are encountered in the renal capillaries, chiefly of the glomeruli, of swine dead of hog-cholera; or of animals infected with the hog-cholera bacillus. In extreme cases there is complete anuria; and it may be impossible to force more than a minimal amount of injecting fluid into the renal vessels. Sections stained with Weigert's fibrin-stain look as if the capillaries had been injected with Berlin blue. Ribbert found similar hyaline thrombi in the kidneys of rabbits inoculated with the S. pyogenes aureus. I have repeatedly found them in various experimental infections, and in human infections. They occur in eclampsia. Bacteria are not necessarily present, so that toxins are probably the underlying causative factor, and for this there is experimental evidence.

Klebs and others have thought that the hyaline material is derived from coalesced and altered red corpuscles. Red corpuscles may in fact be so crowded together, and apparently coalesced, as to appear as nearly homogeneous yellowish cylinders (globular stasis). The genuine hyaline thrombi have the staining reactions of fibrin, and are often continuous with ordinary fibrillated fibrin in larger vessels. Transitions between fibrillated fibrin and the hyaline material can sometimes be seen; but it is often impossible by any staining to resolve the latter into a fibrinous network. If the recent views previously mentioned concerning the origin of platelets from red corpuscles and the participation of these corpuscles in the process of coagulation be accepted, there would be no difficulty in adopting Klebs's hypothesis as to the origin of hyaline thrombi from red corpuscles. Von Recklinghausen and Kriege find evidence that the hyaline substance is derived from leucocytes.

Growth, Metamorphoses, and Organisation of Thrombi.—Thrombi in their growth assume various characters to which special epithets are applied. A thrombus formed from the circulating blood is at first parietal or mural, but by continued growth it may fill the vessel and become an occluding or obstructing thrombus. A primitive or autochthonous thrombus, caused by local conditions, may be the starting-point of a continued or propagated thrombus, extending in the course of the thrombosed vessel and perhaps into communicating vessels. A secondary or encapsulating thrombus is one which starts from an embolus of thrombotic material. A continued thrombus is also often spoken of as

secondary. Thrombi are, with rare exceptions, adherent, at least in places, to the wall of the vessel or the heart. Mural thrombi appear more or less flattened against the vessel wall, or they may project in a globular or polypoid form into the lumen. Their free surface is generally rough. Loose thrombi in the heart are called ball-thrombi.

The thrombus grows in length chiefly in the direction of the current of blood; but it may grow in the opposite direction. The intact and growing end of the thrombus is a flattened blunt cone, usually not adherent to the wall of the vessel; it is sometimes compared in shape to a serpent's head. A venous thrombus extends in the direction of the circulating blood, not only as far as the next branch, but frequently a greater or less distance beyond it, in the form of a mural thrombus. A thrombus is at first soft in consistence and moist; but by contraction and extrusion of fluid it becomes more compact, firmer, drier, and more granular in texture.

Mural thrombi, especially small ones, such as fresh vegetations on the cardiac valves, may occur without any definite arrangement of the constituent elements. Such thrombi may consist almost wholly of platelets; but it is most exceptional not to find at least some admixture with leucocytes and fibrin coagulated *intra vitam.*

The larger white and mixed thrombi often present a typical architecture. The stratified structure has long been known and emphasised. More recently Zahn has directed especial attention to the rib-like markings on the free surfaces,[1] and Aschoff to the internal architecture of white and mixed thrombi. Microscopical sections of these thrombi often show an exquisitely trabecular structure due to irregularly contoured, anastomosing columns and lamellæ, of varying size and shape, which spring at intervals from the wall of the vessel and extend, usually in an oblique or twisting direction, toward the free surface of the thrombus, upon which their extremities form the network of whitish lines or the transverse ribs noted by Zahn. If the thrombus be detached from the inner wall of the vessel, similar projecting lines and dots can be seen on its attached surface and often on the inner lining of the vessel. This trabecular framework of the thrombus is composed of masses of platelets with cortical layers of fibrin and leucocytes, as already described. The whole arrangement is aptly compared by Aschoff to branching coral stems. The spaces between the trabeculæ contain blood which during life may be fluid or may have coagulated; or they may contain only fibrin and leucocytes, or an indefinite mixture of platelets, fibrin and red and white corpuscles. Between the lamellæ and columns bands of fibrin with or without platelets, often stretch loosely and in a curved manner, the concavity of the curve looking toward the axis of the vessel. Aschoff explains the coral-like architecture and the ribbed surface of the thrombus partly by the oscillatory or

[1] A number of writers before Zahn observed the markings on the surfaces of thrombi. Bristowe in 1855 spoke of the "peculiar ribbed appearance" of the surface of cardiac thrombi (*Trans. Path. Soc. London*, vol. vii. p. 141).

wave-like motion of the flowing blood, which, as previously suggested by Zahn, may account for the ribs, and partly by slight irregularities of surface level normally present in the inner lining of vessels. Zahn finds an analogy between the ribs of a thrombus and the ripple-marks in sand at the edge of the sea, or at the bottom of flowing streams. Before Zahn, Wickham Legg, in 1878, described the surface of a cardiac thrombus as "marked by lines resembling the impressions made by the waves on a sandy shore."

The usual explanation of the red and white stratification of mixed thrombi is that the thrombus is deposited in successive layers, of which the red are formed rapidly and the white more slowly. There are manifest difficulties in such an explanation. It is more probable that the red layers are cruor clots formed from blood brought to a standstill. Blood entering crevices, spaces, and clefts resulting from the irregular mode of growth of the thrombus, or from its contraction, or from the blood-stream, often with increase of pressure in consequence of the thrombotic barrier, undermining and splitting the white substance, at first soft and later brittle, of the thrombus, may readily stagnate and clot. Indications of such a splitting of the thrombus by the circulating blood are often seen in horizontal white lamellæ covering red layers and present within them: these lamellæ are apparently split off from the general framework and bent in the direction of the blood-current. The typical architecture of the thrombus may not appear, or may be obscured or destroyed by displacement of its parts through the blood-stream, especially when this is forcible: hence it is often missed in arterial thrombi. White thrombi are, as a rule, microscopically mixed thrombi; and in colour there is every transition from these to thrombi so red that careful examination is required for the detection of the white substance.

In long propagated venous thrombi smaller white thrombus-masses often alternate in a longitudinal direction with longer red ones. The explanation of this is that a primary white thrombus is formed, often starting from a valvular pocket. This becomes an occluding thrombus, and the column of blood reaching to the nearest branch, or to the confluence of two important veins, is brought to a standstill, and forms a red, obstructing thrombus. At the extremity of this, where the blood enters from the branch, another white occluding thrombus may be formed, to be followed again by a red thrombus, and so on. Thrombi are sometimes described as red in consequence of failure to detect the small white autochthonous part of the thrombus. In fact the term mixed thrombus is applied to three different appearances of thrombi: (*a*) an intimate mixture of gray and red substances; (*b*) stratification in successive gray and red layers, and (*c*) red propagated clots consecutive to autochthonous white or mixed thrombi.

In old thrombi various metamorphoses have occurred which obscure or obliterate the typical structure and architecture of the younger ones. The masses of platelets, although they may persist a long time, become

finely granular, sometimes almost or quite homogeneous in texture. They are invaded by fibrin, especially along the edges of spaces and clefts which appear. Notwithstanding these profound changes a certain configuration and a differentiation in staining properties often enable us to recognise the sites of the original columns and lamellæ of platelets. The leucocytes, often at an early date, undergo fatty degeneration and necrosis, their nuclei disappearing both by karyolysis and karyorrhexis. The leucocytic detritus adds to the granular material of the thrombus. The red corpuscles are decolourised and fragmented. The hæmoglobin is in part dissolved and, after organisation begins, is partly transformed into amorphous and crystalline hæmatoidin. These pigmentary transformations impart a brownish red colour to red and mixed thrombi. Fibrin increases in amount and becomes coarse and dense. The part of the thrombus adjacent to the vessel-wall is often converted into compact concentric layers of fibrin at a period when masses of platelets are well preserved nearer the lumen. The hyaline material, which is very frequently found in layers and clumps in old thrombi, may be derived both from fibrin and from platelets; perhaps also from red corpuscles and leucocytes. It may stain well by Weigert's fibrin-stain, or only faintly, or not at all. Small spaces and canals, often containing nucleated cells, may be present in the homogeneous fibrin or hyaline substance (canalised fibrin of Langhans).

Of special importance are the liquefactive softenings which may occur in old thrombi. These are distinguished as simple or bland, septic or purulent, and putrid softenings.

The simple softenings occur in bland thrombi, being especially common in globular cardiac thrombi which, when old, regularly contain in their interior an opaque whitish or reddish thick fluid. This in old days was mistaken for pus, and hence the name puriform softening (purulent cysts). The liquid or pulpy material is the result of granular disintegration and liquefaction of the solid constituents of the thrombus, and consists of necrotic fatty leucocytes, albuminous and fatty granules, blood pigment and altered red corpuscles; the varying red tint of the fluid depending upon the number of red corpuscles originally present in the thrombus. Occasionally acicular crystals of fatty acid are present. This form of softening is probably due to the action of some ferment; it occurs in ordinary bland thrombi, and is distinguished from the infective forms. It is not generally supposed that micro-organisms are in any way concerned in the process: bacteria, however, have been found of late years repeatedly in these thrombi; and it may be that they are not so absolutely unconcerned in simple thrombotic softening as is generally thought to be the case.

There is no question as to the participation of bacteria in the other forms of softening. Septic or purulent softening, met with most frequently in infective thrombo-phlebitis, is a true suppuration; being the result of the accumulation of polynuclear leucocytes with fermentative liquefaction of the thrombus. The leucocytes are attracted in part from

the blood of the thrombosed vessel and in part from the vasa vasorum and surrounding capillaries and veins. Pyogenetic bacteria, most frequently streptococci, are present in the thrombus and the walls of the vessel. Putrid softening is due to the invasion of putrefactive bacteria. Here the thrombus is of a dirty brown or green colour, and of foul odour.

These various softenings often lead to the separation of thrombotic fragments to be transported by the circulation as emboli,—bland, septic, or putrid according to the nature of the process.

White thrombi in veins, far less frequently in arteries, may undergo calcification, forming phleboliths or arterioliths. They are generally approximately spherical, and lie loosely or slightly adherent in the lumen. They are found most frequently in the veins around the prostate and bladder of men, in the plexus pampiniformes of women, and in the spleen.

One of the most interesting adaptive pathological processes is the so-called organisation of thrombi, which is the substitution for the thrombus of vascularised connective tissue. The thrombus itself takes no active part in the process, but behaves as a foreign body. It is gradually disintegrated and absorbed, largely through the activities of phagocytes. The new tissue springs from the wall of the vessel or the heart; the tissue-forming cells being derived both from the endothelium and from other fixed cells in the wall. New vessels spring from the vasa vasorum. Lacunar spaces in the thrombus, or between the thrombus and the vascular wall, may become lined with endothelium, and also serve as channels for the circulating blood. These new vessels may establish communication with the lumen of the thrombosed vessel above or below the thrombus, or on both sides. The new tissue, which at first is rich in cells, becomes fibrous, and contracts. The result may be a solid fibrous plug, or a cavernous structure with large blood-spaces; or, by disappearance of the septa, a restoration of the lumen, with perhaps a few fibrous threads or bands stretching across it, as in the normal cerebral venous sinuses.

There are great diversities in individual cases as to the rapidity of onset and the course of the organising process; these differences depending upon various circumstances, the most important of which are the location of the thrombus, the condition of the wall of the vessel or heart, the general state of the patient, and the presence or absence of infection. In favourable cases the process may be well under way within a week. The wall of the vessel, or of the heart, may be so diseased as to be incapable of furnishing any new tissue; as is usually the case in aneurysmal sacs, and often in varices and in cardiac disease. The presence of pyogenetic bacteria prevents or delays the process of organisation. This process is a proliferative angeiitis. It is this angeiitis which leads to the closure of a vessel after ligation. If the ligature be applied aseptically, and without injury to the internal coats, usually no thrombus is formed, or only a very small one. The formation of a thrombus is of no assistance in securing obliteration of a ligated vessel, in fact it impedes the development of the obliterating endarteritis.

The causes of organisation of thrombi are probably to be sought partly in the influence exerted by the thrombus as a foreign body, and partly in slowing or cessation of the blood-current and lowering of the tension of the vessel-wall (Thoma, Beneke). Whether, in addition, growth of cells may be determined by chemical substances derived from the thrombus is uncertain.

Etiology.—The recognition of the three classes of causes assigned for thrombosis, namely, alterations in the blood, mechanical disturbances of the circulation and lesions of the vascular or cardiac wall, is not of recent date. The dyscrasic theory is the oldest. John Hunter introduced and Cruveilhier elaborated the conception of primary phlebitis with consecutive plugging of the vein; and Baillie, Laennec, Davy and others emphasised stasis as a cause of intravascular clotting. Virchow's name, however, is the one especially associated with mechanical explanations of thrombosis. The experiments of Brücke, showing the importance of integrity of the vascular wall in keeping the blood fluid, led to general recognition of the part taken by alterations of this wall in the etiology of thrombosis.

While it is generally agreed that slowing and other irregularities of the circulation, contact of the blood with abnormal surfaces, and changes in the composition of the blood are concerned, singly or in combination, in the causation of thrombosis, there is much difference of opinion as to the relative importance of each of these factors, and as to the part of each as a proximate, as a remote, or as an accessory cause.

Slowing and other irregularities of the circulation.—Diminished velocity of the blood-current is not by itself an efficient cause of thrombosis. The circulation may be at a low ebb for a long time without the occurrence of thrombi. A stationary column of blood included in an artery or vein between two carefully applied aseptic ligatures within the living body may remain fluid for weeks (Glénard, Baumgarten). Slow circulation, however, in combination with lesions of the cardiac or vascular wall, or with the presence of micro-organisms or other changes in the blood, is an important predisposing cause of thrombosis, and frequently determines the localisation of the thrombus. This is evident from the relative infrequency of thrombi upon diseased patches of the inner coat of large arteries in contrast with their frequency upon similar patches in the small arteries and in the veins; and in general from the predilection of thrombi for those parts of the circulatory channels in which the blood-flow is normally, or as the result of disease, slow. Extensive injury to the walls of arteries may be experimentally produced without resulting thrombosis.

Eberth and Schimmelbusch find that under normal conditions the platelets circulate with the red corpuscles in the axial blood-current, but make their appearance in the outer still zone when the rapidity of the circulation is sufficiently diminished. Moderate slowing is attended by the accumulation of white corpuscles in this zone, while a further slackening of the stream is characterised by fewer leucocytes and more

platelets in the peripheral layer. Mere slowing of the circulation, however, does not suffice to form thrombi; there must be some abnormality of the inner lining of the vessel-wall, with which the platelets are brought into contact, in order to induce the viscous metamorphosis of these bodies essential in the formation of plugs. Hence Eberth and Schimmelbusch conclude that it is only by the combination of slowing of the circulation with changes in the inner lining that the formation of white thrombi can be explained.

Von Recklinghausen attaches more importance to a whirling or eddying motion (Wirbelbewegung) than to mere slowness of the circulation. He has pointed out that eddies are produced when the blood enters normally or pathologically dilated channels from smaller ones, or passes into a cul-de-sac, or over obstructions; and he has considered in an interesting way the special conditions causing this motion and its influence upon the production of thrombi. This irregularity of the blood-current will be referred to again in considering the localisation of venous thrombi (p. 181). Von Recklinghausen's observations make a valuable contribution to our knowledge of the mechanical disturbances of the circulation which favour the development of thrombi.

Thrombi attributed to slowing of the blood-current, often combined with eddying motion of the blood, are called stagnation-thrombi. Of these two groups are distinguished: (*a*) those due to local circulatory disturbances, as from interruption or narrowing of the lumen of vessels by ligation or compression, or from circumscribed dilatations, as aneurysms or varices; and (*b*) marantic thrombi resulting from weakened heart's action, with consequent feebleness of the general circulation. Virchow gave the name "marantic thrombi" to all or nearly all thrombi complicating or following anæmic and cachectic states, general infective diseases—as enteric fever, typhus fever, and the like, and certain constitutional diseases. He considered a condition of marasmus, or great prostration, to be the common underlying factor. As we shall see subsequently, there are serious objections to this explanation of these thromboses, which indeed constitute the class of chief medical interest. The designation "marantic thromboses" for this group is still, however, in common use. Although it is proper in these groups of thrombi to emphasise the mechanical disturbances of the circulation as an important accessory factor, it is evident, from what has been said, that the class of stagnation-thrombi cannot be maintained in the strict sense originally advocated by Virchow. Other factors, especially lesions of the walls of the heart or vessels, enter decisively into their causation.

Contact of the blood with abnormal surfaces. Lesions of the cardiac and vascular walls.—It is universally recognised that the influence of the endothelial lining of the vascular channels in maintaining the fluid state of the blood is of the first importance. This influence appears to be partly physical and partly chemical. The smooth, non-adhesive character of the inner surface of the heart and vessels is the physical property which comes primarily into consideration. Whereas the introduction of

such foreign bodies as threads, or bristles with rough surfaces, into the circulation is an efficient cause of thrombosis, perfectly smooth, indifferent bodies, as small glass balls, may be introduced without causing any coagulation (Zahn). Freund has shown that blood collected with proper precautions in vessels lined with oil or vaseline remains fluid for a long time. Mere contact with a foreign surface, therefore, does not suffice to induce clotting; the result depends upon the character of this surface. Freund concludes that the essential thing is that the surface shall be such as to permit adhesion to occur between it and the corpuscles, particularly the red corpuscles; the normal lining of the blood-vessels being characterised by the absence of this adhesive property. Without adopting Freund's theory of coagulation, which does not here concern us, we can apply, with much satisfaction in the explanation of many thrombi, his observations concerning the importance of adhesive surfaces in causing coagulation. There should also be taken into consideration the damage known to be inflicted by adhesive contact with abnormal surfaces upon platelets or red corpuscles; if these be regarded as the source of the granular material and platelets in thrombi.

Changes, therefore, which impair or destroy the smooth, non-adhesive surface of the normal inner lining of the vessels play an important part in the etiology of thrombosis; and thrombi thus caused may be called adhesion-thrombi. The efficiency of these lesions in causing thrombi is increased if, by projection into the lumen, they obstruct the blood-flow; or by their rough, irregular surface set up an eddying motion of the blood.

Although we have very little definite information about any chemical activities of the normal vascular endothelium concerned in the preservation of the fluidity of the circulating blood, there is evidence that lesions of the intima, through chemical as well as physical influences, may incite thrombosis. That necrotic endothelial and intimal cells may liberate fibrin-ferment is in accordance with both physiological and pathological observations relating to the origin of this ferment from dead or disintegrated protoplasm in general. Reference has already been made to observations of Zenker indicating the coagulative influence of necrotic endothelium, and of the intima deprived of endothelium.

Strong support for a belief in the participation of chemical substances in the causation of certain thrombi due to intimal lesions is to be found in contrasting the effects of mere traumatism with those of traumatism combined with infection of the intima. This has been especially brought out in the experimental studies of valvular lesions of the heart. Aseptic laceration of the cardiac valves generally leads to but slight production of thrombi upon the injured surfaces; whereas the same traumatic lesions, combined with the lodgment and growth of pyogenetic bacteria, are usually attended by the formation of considerable thrombotic vegetations. The differences in the result can hardly be explained by differences in the physical characters of the lesions in the two cases; but we have no definite knowledge concerning the

nature and mode of action of the chemical bacterial products concerned in causing the thrombi. We may draw the conclusion that lesions of the intima, apart from their more manifest characters, may possess certain specific properties especially favourable to the production of thrombi.

The most important of the structural changes of the vascular and cardiac walls which cause thrombosis are those due to inflammation, atheroma, calcification, necrosis, other degenerations, tumours, compression, and injury. Here again may be emphasised the importance of retardation and other irregularities of the circulation in rendering these various lesions effective causes of thrombosis. The aorta, for example, may be the seat of most extensive deforming endarteritis, with irregular projecting calcific plates and ragged atheromatous ulcers, without a trace of thrombotic deposit. The forcible pulsating current prevents the adhesion and accumulation of the formed elements constituting the beginning thrombus, or quickly washes them away. The presence in some instances of white mural thrombi in the aorta upon an intima apparently but slightly damaged indicates the importance of certain specific, although little understood, characters of intimal lesions in association with changes in the blood.

Foreign bodies, which have penetrated the blood-channels and set up thrombosis, have been observed repeatedly in human beings, especially in the heart and abdominal veins. Such accidents have followed swallowing fish-bones, needles, nails, bits of wire and the like. A blood-clot or thrombus in a vessel, or projecting into the lumen from a wound of the vessel, may itself be looked upon as a foreign body, and lead to further extension of the thrombus. There seems to be a certain self-propagating power in a thrombus. Similar effects are produced by the entrance of large parasites, such as distomata, by the invasion of tumour-masses, and by the penetration of parenchymatous cells into the circulatory channels (p. 260).

Infective thrombi. Thrombo-phlebitis.—Phlebitis, as a cause of thrombosis, has reacquired within the last few years so much importance that it is here singled out from other lesions of the vascular wall for special consideration.

In the first half of the present century, mainly through the influence of John Hunter and of Cruveilhier, thrombosis was by many regarded only as an expression of inflammation of the inner lining of the vessels. The material composing the thrombus was considered to be, at least in part, an exudate of coagulable lymph from the inflamed vascular wall. Virchow, by his monumental work on thrombosis and embolism, dating from 1846, reversed this order of things, and made, for the great majority of cases, the thrombus the primary and essential phenomenon, and the inflammation of the wall, if present, a merely secondary effect. Phlebitis disappeared, as a chapter, from works on internal medicine, and thrombosis took its place. Within recent years, and again chiefly through the work of French investigators, the pendulum has swung

back, and phlebitis has once more come to the front as a common and important cause of thrombosis, and resumed an important place in many systematic treatises on medicine. This rehabilitation of phlebitis is due mainly to bacteriological investigations of thrombosed vessels, especially of the so-called marantic thrombi of infective and cachectic diseases.

The distinction between bland thrombi and infective thrombi is an old and important one. The thrombi in septic and suppurative phlebitis, concerned especially in pyæmic processes and surgical affections, were for a long time the chief, indeed almost the only recognised representatives of the class of infective thrombi. There has been a gradual extension of the domain of infective thrombosis, until now many thrombi, previously classified as bland, are considered to be of infective origin. This is notably true of a large number of thrombi, formerly and still often called marantic, complicating many infective diseases, wasting and cachectic conditions, and anæmia. In 1887 Weigert stated that by means of his fibrin-stain he had found unsuspected micro-organisms in marantic thrombi with surprising frequency; and since then there have been numerous similar observations, as well as not a few negative ones. In France the studies of Cornil and his pupils, especially Widal, and of Vaquez have had the greatest influence in developing the doctrine of the mycotic origin of this class of thrombi, and particularly that of primary phlebitis as the cause of these thromboses. It should not be forgotten that Paget, in 1866, contended for the primarily phlebitic nature of thrombosis in gout.

Phlegmasia alba dolens of the puerperium is the prototype of this class of thromboses. In the articles on various infective diseases, particularly enteric fever (see vol. i. p. 817) and influenza (vol. i. p. 683), attention has been called to the occurrence of thrombosis as a complication or sequel. Similar thromboses occur in pneumonia, typhus, acute rheumatism, erysipelas, cholera, scarlatina, variola, tuberculosis, syphilis,—in fact with greater or less frequency in nearly all acute and chronic infections. Likewise in chlorosis, gout, leukæmia, senile debility, and chronic wasting and cachectic diseases, particularly cancer, thrombosis is a recognised complication. The more important associations of thrombosis with these various diseases will be considered more in detail subsequently (p. 191).

These various thromboses, occurring very rarely as primary affections, usually secondary to infective or constitutional diseases, compose the great majority of those of medical, as distinguished from surgical interest. Clinically and anatomically they undoubtedly have much in common. Is there any common etiological point of view from which they may be regarded? Virchow thought so in calling them marantic thrombi, and attributing their causation to enfeebled circulation. The same causative factor still remains the underlying one with those who, like Cohnheim, interpolate nutritive changes in the endothelium between the slow circulation and the beginning of the thrombus.

Impaired circulation cannot serve as a common etiological shelter for this whole class of thromboses. There is no definite and constant relationship between the condition of the circulation and the occurrence of these thrombi. While many appear during great debility, others of the same nature, and often in the same disease, occur when the heart's action is not notably weak. Thrombosis may ensue early in influenza. It is oftener a sequel than an accompaniment of enteric fever. On the other hand, the circulation may be extremely feeble for days without the appearance of thrombosis.

Many of these so-called marantic thrombi are unquestionably of infective origin. Vaquez, in his monograph on phlebitis of the extremities, published in 1894, has brought together the results of the observations of others, and especially those of his own and Widal's investigations, which demonstrate that bacteria are often present in these thrombi and in the adjacent vascular wall. Since the appearance of Vaquez' monograph there have been a number of confirmatory observations. Widal emphasises the importance of searching for bacteria in fresh thrombi, and in the autochthonous part of the thrombus and the adjacent wall of the vessel. The largest contingent of positive results has been furnished by the examination of puerperal thrombi,—many of which indeed are examples of septic thrombo-phlebitis, and of the marantic thrombi of chronic pulmonary tuberculosis; but bacteria have also been found in thrombi complicating or following typhoid fever, influenza, pneumonia, cancer, and other infective and cachectic conditions.

In relatively few instances has the specific micro-organism of the primary disease, as the typhoid or the tubercle bacillus, for example, been present in the thrombus; more frequently secondary invaders, especially streptococci and other pyogenetic bacteria, have been detected: so that the thrombosis is considered to be oftener the result of some secondary infection than of the primary one. Colon bacilli have been found in typhoidal and other thrombi; but as these bacteria are found so commonly in the blood and organs after death from all sorts of causes, no great importance can be attached to their mere demonstration without some further evidence of their pathogenetic activity. As might be expected, streptococci are the bacteria found most frequently in puerperal thromboses. Singer believes that gonorrhœal infection is also a possible factor.

Not only in thrombi of infective diseases but also in cachectic thromboses have bacteria, and here again most frequently pyogenetic forms, been demonstrated. Nor is this surprising when we consider the frequency of secondary infections in chronic diseases, especially as a terminal event; as has been clearly brought out in the analyses, by Flexner, of the autopsies at the Johns Hopkins Hospital, where bacteriological examination is a routine procedure at the post-mortem table. Many of these infections are unsuspected during life.

The supposition that in all of these cases the bacteria are accidentally or secondarily present, and in no way concerned in the causation of

the thrombi, is extremely improbable. They are often in such number, in such arrangement and associated with such lesions, that they must have multiplied in the thrombus and in the vessel wall.

The problem whether the bacteria have led to thrombosis by first invading the vascular wall and setting up inflammation is not solved by the mere demonstration of their presence. Certainly, in some instances, this sequence of events is plainly indicated by the microscopical appearances; but in many it is impossible to decide to what extent inflammatory changes in the wall antedated the thrombus, for the latter, especially when infected by bacteria, induces a secondary angeiitis. Opportunities to study very recent infective marantic thrombi with reference to this point are not common.

In a case, which I examined, of multiple venous thrombosis complicating leucocythæmia, there was a primary mycotic endophlebitis with secondary thrombosis. There was a secondary streptococcus infection. In the intima of the thrombosed vessels were numerous scattered foci in which large numbers of streptococci were present. In these areas there was necrosis of endothelial and other intimal cells, with proliferation of surrounding cells and many polynuclear leucocytes. These foci formed little whitish elevations capped with platelets, fibrin, and leucocytes; the whole presenting an appearance similar to that of endocardial vegetations. There was marked nuclear fragmentation both in the infected intima and in the thrombus. Fresh mixed thrombi, containing fewer streptococci, were connected with these phlebitic vegetations. Although the vasa vasorum were hyperæmic, and were the seat of a moderate migration of leucocytes, streptococci were absent from the adventitia; and the appearances spoke decidedly for the direct penetration of the streptococci from the circulating blood into the intima. I have examined three other similar cases. A similar form of mycotic endophlebitis has been described by Vaquez (endophlébite végétante). In other cases the intima is more diffusely inflamed. After a short time there is no distinct line of demarcation between the thrombus and the intima, and all of the coats of the vessel are more or less inflamed.

Although the bacteria found in the intima may gain access from without through the vasa vasorum, or the lymphatics, it is probable that in the class of cases here under consideration they more frequently enter directly from the blood circulating in the main channel. There may be very extensive bacterial inflammation of the venous wall, even with bulging of the intima into the lumen, without any thrombosis.

We do not possess sufficiently numerous and careful bacteriological examinations of the thrombi of infective and wasting diseases to enable us to say in what proportion of cases they contain micro-organisms. It is certain that in many instances such examinations have yielded negative results. It is quite possible that in some of these negative cases bacteria, originally present, have died out; but although by some authors much use is made of this explanation, it is not in general a satisfactory

one. Many of the examinations were of thrombi sufficiently recent to exclude this possibility.

To explain these non-bacterial cases, the French writers assume the existence of a primary toxic endophlebitis, the toxins being either of bacterial origin or derived from other sources. Ponfick, many years ago, called attention to the occurrence of degenerations of the vascular endothelium in infective diseases; and there can be no doubt of the frequency of both degenerative and inflammatory changes of the intima in toxic and infective conditions.

A lesion which I have seen in the intima of veins (less frequently of arteries) in typhoid fever, diphtheria, variola, and other infective diseases, is a nodular, sometimes a more diffuse, accumulation of lymphoid and endothelioid cells beneath the endothelium. These cells, as well as the covering endothelium, may undergo necrosis; indeed the appearances sometimes suggest primary necrosis with secondary accumulation of wandering cells and proliferation of fixed cells. These foci are not unlike the so-called lymphomatous nodules found in the liver in typhoid and other infections. They may unquestionably be the starting-point of thrombi, as has been shown by Mallory in his study of the vascular lesions in typhoid fever. Although this form of endophlebitis or endarteritis resembles that demonstrably caused by the actual presence of bacteria in the intima, bacteria are often absent, even in the fresh lesions; so that it is reasonable to suppose that the affection may be caused by toxins. I think that this toxic endangeiitis is of importance in the causation of thrombosis complicating infective and cachectic states.

There are, however, instances of so-called marantic thrombosis where no visible alteration of the intima can be made out at the site of the thrombus, or only the slight fatty degeneration of the endothelium which is such an extremely common condition that it does not afford a satisfactory explanation.

It is obvious that bacteria are likely to find especially favourable opportunities to gain lodgment, and toxic substances to do injury, in situations where the blood-current is slow and thrown into eddies; but the localisation in these situations of thromboses complicating infective and chronic diseases has perhaps been unduly emphasised. These thromboses may occur elsewhere, even in the aorta and larger arteries. Pre-existing diseases of the veins, especially chronic endophlebitis and varicosities, are conditions predisposing to infective and cachectic thromboses.

While we are justified in assigning a far more prominent place to the agency of micro-organisms and to primary phlebitis in the etiology of thrombosis than, until recent years, has been customary since Virchow's fundamental investigations, recent attempts to refer all thromboses, formerly called marantic, to the direct invasion of micro-organisms and to phlebitis go beyond demonstrated facts. We have not at present any satisfactory bacteriological and anatomical substratum

for so wide a generalisation. The whole field, although difficult, is an inviting and fruitful one for further investigation. The clinical arguments in favour of the phlebitic origin of thrombosis will be considered below (p. 212).

What has been said regarding the relation of phlebitis to thrombosis complicating infective and constitutional diseases applies also to that of arteritis to the similar arterial thromboses which, although less common than the venous, are more frequent than was formerly supposed; this will appear when we take up the association of thrombosis with particular diseases (p. 191).

It is of course understood that the preceding remarks on the relation of phlebitis and arteritis to thrombosis relate only to the medical thromboses, and not to the septic and suppurative thrombophlebitides of the surgeon, of the bacterial origin of which there is no question; although these latter may be concerned in diseases, such as suppurative pylephlebitis, which are in the province of the physician.

Chemical changes in the blood. Ferment-thrombi.—The old ideas of chemical changes in the blood as causes of intravascular clotting, embodied in such terms as acre coagulatorium, hyperinosis, inopexia, are now of historical interest only. There appears to be no definite and constant relation between the amount of fibrin obtainable from the blood, or the rapidity of its coagulation in the test tube, and the occurrence of thrombosis in human beings. Peripheral thrombosis is a less common complication of pneumonia and acute articular rheumatism, which are characterised by high fibrin-content of the blood, than of enteric fever and certain cachectic states in which the fibrin-content is approximately normal or reduced.

In dogs whose blood was rendered incoagulable by injection of "peptone" (albumose) Schimmelbusch produced platelet-thrombi experimentally. On the other hand, Sahli with Eguet observed no collection of platelets or formation of thrombi around hog's bristles or silk threads inserted into the jugular veins of rabbits having incoagulable blood from injection of leech extract; although control experiments regularly gave positive results. These latter experiments show that chemical changes in the blood may influence the process of thrombosis.

The main support of the belief entertained by some that the liberation of fibrin-ferment in the general blood-stream is an important cause of human thrombosis, is based on the results of experiments which demonstrate that the injection of various substances into the circulation may cause intravascular clotting. The most important of the substances which have been observed to produce this effect are laky blood (Naunyn), biliary salts (Ranke), ether (Naunyn, Hanau), fresh defibrinated blood (Köhler), emulsions or extracts from cells, especially lymphoid cells (Groth, Wooldridge), transfusion of blood (Landois, Ponfick), and snake-venom (C. J. Martin, art. "Snake-poison and Snake-bite," vol. iii. p. 819). The coagulating effect of laky blood is attributable to the stromata of red corpuscles rather

than to dissolved hæmoglobin (Wooldridge). The coagulating principle here, as well as of the various tissue-extracts, is believed to be a nucleo-proteid which, by combination with calcium, forms the fibrin-ferment. It is to the presence of this ferment or the subsequent liberation of the ferment that the dangerous intravascular clots following the injection of defibrinated blood or the transfusion of foreign blood are due. The coagulative effect of snake-venom under certain conditions is referred by Halliburton to proteoses free from phosphorus, and therefore not nucleo-proteids. The action of snake-venom upon coagulation is probably analogous to that of various toxic albumoses, bacterial and vegetable. They are in general to be ranked among anti-coagulating substances; but the result varies with the dose, the manner of injection, and other circumstances. Wooldridge has shown that thromboses are particularly prone to occur in the territory of the portal system after the injection of various substances favouring coagulation. Fibrin-ferment may be used up in the process of intravascular clotting, so that after this has taken place the remaining blood may be incoagulable.

Interesting as these experimental results are to the physiologist, and with reference to the theories of the coagulation of blood, it is difficult to utilise them in any satisfactory way in the explanation of ordinary human thrombosis. Most of the experimenters make no statement as to the microscopical structure of the intravascular clots, which are described generally as soft, dark red masses; and they seem to identify them with ordinary human thrombi, being apparently not familiar with the researches on the peculiar constitution of the latter. Some of the substances used for the experiments cause precipitates in the blood, and many are very destructive to the red corpuscles. Hanau, however, has shown that masses of platelets may be present in these clots.

Conditions analogous to those set up in these experiments may occur in human beings; but they are, so far as we know, most exceptional. Especially do we lack satisfactory observations, in cases of thrombosis in human beings, of increase of fibrin-ferment in the blood. Considerable quantities of fibrin-ferment, more than are likely to be liberated under any probable circumstances in man, can be injected into the circulation without causing coagulation. Still it is possible that the mechanism by which this excess of fibrin-ferment is neutralised and coagulation prevented may be paralysed under certain conditions. There are certain instances of rapidly-formed red thrombi in vessels with apparently normal walls which, in the absence of other explanation, it would be very convenient to refer to ferment-intoxication. Köhler and Hanau consider that many thrombi, especially those complicating infective and cachectic states, are best explained by supposing a liberation of fibrin-ferment in the blood, and they call them, therefore, ferment-thrombi.

Hayem designates as thrombi from precipitation (thromboses par précipitation) many which others call ferment-thrombi; especially those

following injection of various destructive substances into the circulation, and those caused by burns and freezing.

Silbermann and others assert that thrombosis, particularly multiple capillary thrombosis, plays an important part in extensive superficial burns, and in poisoning with various substances destructive to the blood corpuscles, such as anilin, potassium chlorate, arsenic, phosphorus, sublimate, carbonous oxide, illuminating gas. These views need further confirmation before they can be accepted, as several observers have obtained only negative results in searching for thrombi in the same class of cases.

Notwithstanding the lack of a substantial basis of demonstrated facts for the opinion that human thrombosis is often caused by liberation of fibrin-ferment in the general blood-stream, it would be quite unreasonable to suppose that chemical changes of the blood are without influence upon the occurrence of thrombosis in man. Indeed, in infective and toxic conditions such changes are doubtless the underlying factors. Both the circulatory disturbances and the alterations in the vascular wall to which we attribute the production of thrombi are the result of damage done to the heart and vessels by bacterial and other toxins. More than this, there is good reason to believe that alterations in the formed elements of the blood, caused directly or indirectly by toxic substances, are of great significance in the etiology of thrombosis. The platelets are in all probability cell-derivatives; and we may well suppose that damage inflicted upon leucocytes and red corpuscles may favour their production, and that, in consequence of abnormal composition of the plasma, the platelets themselves may more readily undergo viscous metamorphosis, and form plugs. In view of recent observations in favour of the origin of platelets from red corpuscles, the studies of Ehrlich, Maragliano, von Limbeck, and others, concerning degenerations and increased vulnerability of these corpuscles in various diseases, are of interest with reference to thrombosis; but it must be confessed that we cannot at present make more than a hypothetical application of these results to the explanation of certain forms of thrombosis. To discuss here further the hypotheses upon this subject would be barren of any useful result.

Increase of blood-platelets.—In view of the essential part taken by blood-platelets in the formation of thrombi, it is important to inquire whether thrombosis can be brought into any relation with a pathological increase of these elements. Some observations of the existence of such a relationship are highly suggestive.

Especial difficulties are encountered in the efforts to enumerate the platelets on account of their small size and their viscid consistence, which causes them to clump together. Brodie and Russell give, as the norm, one platelet to 8·5 red corpuscles; or about 635,000 per cubic millimetre. This estimate is considerably higher than that obtained by others, probably, however, by less accurate methods. Van Emden gives as the average for human beings in health 245,000; which corresponds fairly well with

the figures of Hayem, Cadet, Afanassiew, Muir, Fusari, and Determann, but is lower than those of Laker and Prus.

There is considerable divergence of statement as to the number of platelets in different diseases. This number is markedly increased in chlorosis (Muir), of which thrombosis is a well-recognised complication. The platelets are increased in post-hæmorrhagic anæmia (Hayem), which is one of the remoter causes of thrombosis. There is evidence that hæmorrhage after childbirth, and in the course of various diseases, favours the occurrence of thrombosis. Several observers have found the platelets reduced in number in pernicious anæmia, which, unlike chlorosis, is rarely, if ever, complicated by thrombosis (Hayem, Birch-Hirschfeld, Beugnier-Corbeau). In purpura hæmorrhagica there is extreme diminution of platelets, sometimes amounting to total absence (Denys, Hayem, Ehrlich, van Emden), which constitutes the only demonstrated morphological change of the blood in this disease. In febrile infections there is often a correspondence between leucocytosis and the number of platelets. Thus in influenza, pneumonia, erysipelas, meningitis, and septic infections the number of platelets is often increased, in severe cases sometimes diminished; whereas in enteric fever and malaria it is diminished (Hayem, Reyne, Türk, Muir, van Emden). The disappearance of leucocytosis is sometimes followed by increase of platelets. In view of the greater frequency of thrombosis as a sequel than in the course of many acute diseases, the recognition by Hayem of a platelet crisis (crise hématoblastique) is interesting. After the crisis or subsidence of certain infective diseases Hayem observed a rapid and marked increase in the platelets. This was noted after pneumonia and enteric fever. Platelets are said to be often increased toward the end of pregnancy and after delivery (Hayem, Cadet). In various cachectic conditions, in tuberculosis, and, in general, in states of bad nutrition, increase is the rule. Dr. Muir finds that in spleno-medullary leucocythæmia the platelets are notably increased, but not in the lymphatic form (art. "Leucocythæmia," vol. v. p. 640). In chronic passive congestion, due to heart disease, the platelets are said to be diminished (van Emden). An increase of platelets in various conditions in which they are usually diminished can often be attributed to complications. Upon the whole there is much in support of the view that increase of platelets is an index of lowered resistance of the red corpuscles.

It is fair to say that some of the foregoing statements regarding the condition of the platelets in various diseases need further confirmation, and that in general the subject is difficult and has been insufficiently investigated. Nevertheless we cannot fail to have our attention arrested by a parallelism, in many instances, between disposition to thrombosis and increased number of platelets; although in others no such relationship is apparent. It must suffice to call attention to this parallelism, for we are ignorant of the underlying factors.

It hardly need be said that the mere increase of platelets is insufficient to explain the occurrence of thrombosis. We are brought back

here, as elsewhere, to disturbance of the circulation and changes in the vascular walls as the determinants of the localisation of thrombi; while we must recognise changes in the chemistry and morphology of the blood as important predisposing causes.

Localisation.—Thrombosis may occur in any part of the circulatory system. We distinguish therefore arterial, venous, capillary, and cardiac thrombi. Lymphatic vessels may likewise become plugged with fibrin, leucocytes, or foreign material; such as tubercle, cancer, or red corpuscles.

Arterial thrombi.—The majority of arterial thromboses are caused by some local injury or disease of the arterial wall, or by the lodgment of an embolus. Especially important are the arterio-sclerotic thromboses of the brain, heart, and extremities.

Here may be mentioned the varying relations of arterial thrombosis to *gangrene* of the extremities. Thrombosis of arteries, as well as of veins, may be secondary to varieties of gangrene which are not caused by primary plugging of the arteries. Senile gangrene is caused either by embolism, which may lead to thrombosis, or by arterio-sclerosis, usually associated with thrombosis. In various infective and chronic wasting diseases gangrene may result from primary arterial thrombosis of the class often called marantic. Many of these thromboses are infective in origin; but we have not sufficient information to warrant the assertion that all are caused by micro-organisms.

Of especial interest is the relation of thrombosis to certain forms of so-called "spontaneous" gangrene which may occur in middle life, or even in the young, and are often preceded by definite symptoms indicative of gradual occlusion of the arteries. Von Winiwarter concluded from his examinations of several cases that the primary disease is an obliterating endarteritis resulting in complete closure of the affected vessels. Zoege von Manteuffel, however, finds that thrombosis participates, in an interesting way, in the gradual occlusion of the arteries. According to him, by the deposition and organisation of successive layers of parietal thrombi, the arteries, which are usually the seat of a primary sclerosis, gradually become filled with vascularised connective tissue. Haga considers this endarteritis thrombotica to be syphilitic. Hoegerstedt and Nemser believe that, in general, the deposition and organisation of parietal thrombi are common and important processes in angio-sclerosis. Von Recklinghausen has described hyaline thrombosis of small arteries in spontaneous and arterio-spastic gangrene.

The *action of infective agents* in the causation of focal and diffuse diseases of the arteries is receiving constantly increasing attention. The occurrence of acute and chronic arteritis as a result of various infective diseases—as enteric fever, typhus fever, acute articular rheumatism, variola, scarlatina, pneumonia, endocarditis, septicæmia, syphilis, tuberculosis, leprosy—is now so well established that it is reasonable to believe that the arterial thromboses complicating or following these diseases are often referable to an infective arteritis.

It cannot be doubted that not a few cases reported in literature as primary arterial thrombosis are to be attributed to embolism which was overlooked. The possible sources of emboli for the aortic system can be usually controlled much more readily than those for the pulmonary arteries; for the latter sources embracc all the systemic veins. These veins may contain mural thrombi, or in places occluding thrombi, which give no signs of their presence. The possibility that an cntire thrombus may be detached and transported by the blood-current, so that its original location cannot be determined, is also to be considered. But, after all has been said, it is carrying scepticism to an unjustifiable extreme to refuse to admit the occurrence of primary arterial thrombosis in infective, cachectic, and anæmic states, under circumstances where the localisation cannot be attributed to arterio-sclerosis or other pre-existing arterial disease. Mr. Jonathan Hutchinson has recently reported observations of rapid thrombosis of arteries without obvious disease of the walls.

The most frequent site of arterial thrombosis is in the extremities, and far more frequently in the lower than the upper. Arterial thrombosis, unlike venous, occurs on the right side as often as on the left. Other situations, more or less common, are the cerebral, pulmonary, coronary of the heart, mesenteric arteries, and the aorta and its primary branches.

Venous thrombi.—These may result from local causes, such as traumatism, compression, phlebitis, phlebo-sclerosis, varix (266), inflammation or other lesion of surrounding parts, and eonnection of venous terminals with septic or gangrenous foci.

Vascular thromboses due to general causes are, in the great majority of cases, situated in veins; and to this group the chief medical interest attaches. In special characters of the venous circulation we must seek the explanation of the greater effectiveness of these general causes in veins than in arteries. The physiological peculiarities, partly general and partly local, which come especially into consideration, are—the slower mean speed of the blood in veins than in arteries; the low blood-pressure; the flow from smaller into larger channels; the absence of pulsation; the presence of valves; fixation of the venous wall in certain situations to fasciæ and bone; the existence in some places of wide sinuses and ampullar dilatations; the agency of certain subsidiary forces, such as muscular contraction and movements of the limbs, in assisting the flow in the veins; the composition of venous blood, particularly the higher content of CO_2, and perhaps the functions of the capillaries and small veins in the production and absorption of lymph. It is obvious, without detailed explanation, that some at least of these special characters must render the venous system much more favourable than the arterial to the occurrencc, undcr the general conditions known to dispose to thrombosis, of retardation of the blood-current; eddying motion of the blood, and damage to the vascular wall from impovcrished and insufficient blood-supply, or prolonged contact with micro-organisms and toxic substances, the agency of which in the etiology of thrombosis has alrcady bccn considcred.

The best evidence that these mechanical conditions determine the localisation of the majority of thrombi of infective, anæmic, and cachectic diseases is afforded by the marked preference of such thrombi for situations where these conditions are in the highest degree operative. The tendency of venous thrombi to start from valvular pockets has already been mentioned. It is important to note that thrombi due to general causes, unlike those starting from local septic foci, do not begin in the rootlets, but originate usually in the main venous trunks of a member. The very large veins are unusual primary seats of marantic thrombi. Beginning as a rule in a sinus or medium-sized vein, the thrombus may grow centrally into large veins; as from the femoral into the iliacs and vena cava, and peripherally into small veins, not, however, generally reaching the smallest veins. The favourite starting-point of so-called marantic thromboses of the cerebral sinuses is in the middle of the superior longitudinal sinus at the top of the cranial cavity, whence the thrombus may extend forward, but tends especially to grow toward the torcular Herophili, and into other sinuses and into the cerebral veins. There is, however, no rigid rule in this matter. The plug may begin in other sinuses, or even in the cerebral veins.

In extensive thromboses, such as occur especially in veins of the thigh and leg, it is sometimes difficult to determine the point of origin of the thrombus, and the exact manner of its propagation. Often, however, decisive information can be gained by careful attention to features indicative of the age of thrombi, as already described (p. 163). Thus the autochthonous part of the thrombus is gray, or reddish gray, and firmly adherent; the continued part often red and more loosely attached, and the older parts frequently softened or liquefied in the centre. By observation of such points as these, the common assumption that a thrombus, occupying continuously both large and small veins, began in the most distal veins and grew thence into the larger channels, can often be shown to be erroneous. An occluding thrombus may lead to such disturbances of the circulation as to cause the formation of discontinuous multiple thrombi on both the central and the peripheral sides, and these may become connected by red or mixed thrombi. In short, the modes of extension of thrombi are sometimes complicated, and not readily unravelled.

The so-called law of Lancereaux was enunciated by him in 1862 as an explanation of the common site of thrombi in the cerebral sinuses, and at the summits rather than at the peripheries of the extremities; his rule is as follows:—"Marantic thromboses are always formed at the level of the points where the blood has the greatest tendency to stasis, that is, at the limit of the action of the forces of cardiac propulsion and of thoracic aspiration." There are serious physiological objections to the physical conceptions of the circulation underlying this so-called law, which in any event cannot be accepted in the exclusive form given to it by Lancereaux. Wertheimer has shown that the effect of thoracic aspiration upon the venous circulation extends to

remote parts of the saphenous vein by the side of the tendo Achillis. As the collective sectional area of the veins steadily diminishes from the capillaries to the heart, the average speed of the blood must be greater in the large veins than in the small ones, if the circulation is to continue for any length of time; and this remains true even when the energy of the blood-current is feeble.

Much more satisfactory, it seems to me, is the explanation offered by von Recklinghausen, of which mention has already been made (p. 167). This explanation places the chief emphasis upon the eddying movement (Wirbelbewegung) of the outer lines of flow of the blood-stream when there are counter-currents, or when the blood with retarded flow passes from smaller into larger channels or over obstructions, or especially into spaces relatively too wide for the received volume of fluid. Especially favourable for the appearance of this irregularity of the circulation are the ampullar dilatations just above the insertion of the venous valves, the intracranial sinuses, and the femoral vein near Poupart's ligament, which, in consequence of fixation to bone or fasciæ, cannot readily adjust themselves to a lessened volume of blood, and in which counter-currents are set up by the obtuse or right angles at which blood is received from some of the tributary veins. The trabeculæ which cross the cerebral sinuses may be a contributory factor. Similar irregularities of the blood-flow must occur with feeble circulation in other situations, as in the pelvic venous plexuses, where wide channels are intercalated between smaller ones, in the recesses of the heart, and in aneurysms and varicose veins. Von Recklinghausen has pointed out that the plexus-like arrangement, the entrance of small veins into large ones, and the close apposition of artery and vein render branches of the renal veins in the kidney susceptible to irregular blood-currents.

The greater frequency of venous thrombosis in the left leg than in the right is attributable to the more difficult return-flow from the former, in consequence of the greater length and obliquity of the left common iliac vein and its passage beneath the right common iliac artery. It has been suggested that pressure upon this vein by a distended sigmoid flexure or rectum may likewise contribute to slowing of the blood-current upon this side. The preponderance of thromboses of the left axillary and brachial veins over those of the right is attributed in a similar way by Parmentier; that is, to the greater length and obliquity of the left innominate vein.

As has already been urged, these mechanical disturbances of the circulation are not, by themselves alone, efficient causes of thrombosis. They simply make certain parts of the vascular system seats of election for thrombi. It is quite possible to exaggerate their function in the etiology of thrombosis. The presence of micro-organisms or other changes in the blood may induce lesions of the vascular wall in any part of the circulatory system; and primary thrombi may be formed in situations apparently the most unpromising, so far as the circulatory

conditions are concerned; as for instance in the pulmonary veins and in the venæ cavæ near the heart.

Capillary thrombi.—The blood in the capillaries remains fluid, even with extensive venous and arterial thrombosis, unless necrosis or gangrene of the tissue ensue, in which case, as in infarctions, the capillaries are always plugged. The interesting fibrinous and hyaline thromboses of the capillaries have already been considered (p. 160).

Cardiac thrombi.—There is no stranger chapter in the history of pathology than the story of cardiac polypi, from the first observation of fibrinous clots in the heart by Benivieni, in the fifteenth century, until the end of the last century. It is full of warnings against the uncritical use of post-mortem findings. The cardiac polyps of the old writers were, for the most part, nothing more than ordinary colourless post-mortem clots. Nor has the error of confounding these with genuine thrombi wholly disappeared from medical literature even at the present day. These moist, pale, yellowish, smooth, elastic, uniform, more or less translucent, fibrinous clots, softer or firmer according to their content of serum, non-adherent though entangled with muscular columns and trabeculæ, often showing moulds of the valves or other projecting surfaces with, at least, some red cruor clot at their most dependent parts—such clots, membranous, polypoid, band-like, or filling the right cavities of the heart and sending worm-like offshoots into the vessels, should never be mistaken for the drier, opaque, gray or reddish gray, granular, more friable, usually much smaller, adherent, often centrally softened or stratified thrombi.

Although there is a common impression that these fibrinous clots are formed during the death agony, I know of no good reason for such a view. It is much more probable that they are analogous to the buffy coat of clots in shed blood, and are formed after death, when coagulation does not set in until the red corpuscles have settled from the plasma. Liberation of fibrin-ferment, fibrin-content of the blood, sedimentation-time of red corpuscles and coagulation-time,[1] all variable elements, are the leading factors which determine the production of these colourless clots. Most striking examples of colourless clots are found after death from pneumonia and acute articular rheumatism, where the fibrin-content is high, the sedimentation-time rapid, and the coagulation-time slow. The whole doctrine of death from "heart-clot" in these and other acute diseases is based, in my opinion, upon mistaken interpretation of fibrinous post-mortem clots.

The *fresh vegetations* of endocarditis are not generally included in the consideration of cardiac thrombi. Still they are genuine thrombi, and

[1] By "fibrin-content" is meant the amount of fibrin yielded by the blood, and is not of course to be understood as implying the pre-existence of fibrin in the blood. The rapidity of coagulation is an element which is more or less independent of the total yield of fibrin. Red corpuscles settle from plasma or from serum with varying degrees of rapidity in different specimens of blood. Clots also vary much as to their contraction and the separation of serum. Although in using such an expression as "coagulability of the blood" these factors are often confounded, it is important that they should be distinguished.

there is no more favourable situation for the study of the formation of mycotic thrombi than the acutely inflamed heart-valve. The first step is the invasion of bacteria, as a rule directly from the blood in the cardiac cavities, into the endothelial and subendothelial layers. The surrounding cells undergo rapid necrosis with karyorrhexis; and simultaneously are deposited upon the damaged spot masses of conglutinated platelets followed by leucocytes and fibrin, these masses forming the vegetations. Proliferation of the subendothelial and adjacent cells quickly follows, polynuclear leucocytes migrate into the area, and before long new vessels with organisation of the thrombus make their appearance. A process essentially the same may occur not only in the mural endocardium but also in arteries and veins (vegetative arteritis, vegetative phlebitis, p. 172).

Putting aside these endocardial vegetations, it has been customary to consider the conditions leading to cardiac thrombosis as essentially identical with those of peripheral venous thrombosis, but there are differences. Cardiac thrombi are found especially in association with chronic diseases of the heart, lungs, arteries, and kidneys; in all of which, with the exception of pulmonary tuberculosis, peripheral venous thrombosis is uncommon. On the other hand, most of the acute infective diseases, as enteric fever, influenza, pneumonia, which are so important in the etiology of venous thrombosis, are in general of less relative importance in the causation of cardiac thrombosis, although it may occur in these diseases. In cachectic states, especially phthisis and cancer, the conditions as regards the incidence of cardiac and of venous thrombi are more nearly identical, for here thrombi are often enough found in the heart; particularly when there is well-marked fatty degeneration. Cardiac thrombosis stands in no such peculiar relation to chlorosis and gout as does venous thrombosis, although its occurrence in these diseases is not unknown. The great field for cardiac thrombi is afforded by diseases of the valves and walls of the heart, and especially by dilatation of one or more of its cavities with cardiac insufficiency (asystole of the French school); conditions which, in spite of the great retardation of the venous flow, are not often attended by peripheral venous thrombosis, unless in association with diseases known to dispose to the latter.

The seats of election for cardiac thrombi are the auricular appendices and the ventricular apices between the columnæ carneæ; the particular situation varying as the cause may affect the whole heart, or only one side, or one cavity. In cardiac insufficiency from general or local causes these recesses and pockets must offer the best possible conditions for slowing of the blood-current, and especially for the formation of eddies. That there is no actual stasis of the blood is shown by the gray or reddish gray colour of the thrombi.

The familiar *globular thrombi* (végétations globuleuses of Laennec) are by far the commonest form of cardiac thrombus. Varying in size usually from a pea to a hazel-nut they may attain the size of a hen's egg. They are usually multiple, and neighbouring ones are connected

by an adherent subtrabecular thrombotic meshwork or membrane, of which they constitute sessile or pedunculated spheroidal or ovoid projections. Their surface may be smooth, or marked by delicate lines or ribs; and their interior is usually converted into an opaque, gray, or brownish red grumous fluid, so that the whole resembles a cyst with puriform contents. The liquefaction is of the bland variety already described (p. 164). Although the projecting covering of these cysts is often only a thin shell it rarely bursts. These thrombi may, however, be the source of emboli. Hearts containing these thrombi are often the seat of fatty degeneration. Usually no localised mural disease is to be detected with the naked eye beneath these thrombi, although the microscope generally shows degeneration or defect of the endothelium. It is most exceptional for any trace of organisation to be present in these globular thrombi.

Calcification of cardiac thrombi is a rare event. Delépine has described very fully a cardiolith, and has collected reports of similar cases. Some of these are probably phleboliths in or derived from varicose veins which Wagner, Zahn, and Bostroem have described in the wall of the heart, particularly in the septum auriculorum.

Somewhat different as a rule are the *mural thrombi* found on areas of circumscribed disease of the heart wall; as on infarctions, fibroid patches,[1] and gummata, and in partial aneurysm. These may be identical in appearance with the ordinary globular cysts; but often they are flat or polypoid, stratified, and more intimately incorporated with the cardiac wall.

Cardiac thrombi may be in the shape of massive or of elongated polypoid formations, occupying a large part of one of the cavities, and extending even through valvular orifices into adjacent cavities or vessels. One of the cavities, usually a dilated auricle, may be nearly filled with a massive laminated thrombus, as in a case reported by Osler which I examined. There is much resemblance between the clot in these cases and that found in aneurysms.

Apart from endocardial vegetations not much is known of *infective thrombi* in the heart, although it is probable that they occur more frequently than is suspected. In a child dead of scarlatina I found, in association with streptococcal mitral endocarditis, softened thrombi containing streptococci in the right auricular appendix. There are a few scattered reports of the discovery of bacteria in cardiac thrombi. Particularly interesting are the observations of Weichselbaum, of Birch-Hirschfeld, and of Kotlar, of tubercle bacilli in white cardiac thrombi. Birch-Hirschfeld found in a case of extensive genito-urinary and chronic pulmonary tuberculosis a white organised thrombus in the appendix of the right auricle which contained many tubercle bacilli and numerous tubercles. In these and similar cases there is difficulty in determining

[1] It is interesting to note that in 1809, Allan Burns in his classical work on *Diseases of the Heart*, in recording his observations on angina pectoris with calcification of the coronary arteries and polypi in the left ventricle, called attention to the relations between disease of the coronary arteries and cardiac thrombosis. He thus anticipated Weber and Degny, and other recent writers, who have emphasised the occurrence of cardiac thrombi in angio-sclerotic hearts.

whether the bacteria are the direct cause of the thrombosis, or are secondary invaders. Kotlar interprets his case as the development of miliary tubercles in an organised thrombus.

As there are unquestionable instances of finding emboli derived from venous thrombi in the right heart, the possibility of a thrombus arising secondarily from such an embolus in this situation may be admitted; but I know of no convincing example.

Ball-thrombi, loose in the left auricle, are rare forms of cardiac thrombi. The first observation which I have found of such a thrombus was published by William Wood in 1814, in Edinburgh. As in other typical cases, the loose thrombus was in the left auricle and there was extreme mitral stenosis. The patient, a girl 15 years old, had the regular symptoms of chronic valvular disease. Death was not sudden. Wood thus describes the appearances: "The substance occupying the sinus venosus of the left auricle, when particularly examined, was found to be of a darkish red colour, in form completely spherical, measuring rather more than an inch and a half in diameter. It felt firm, but elastic; the surface was everywhere smooth and polished, but having a singularly clotted appearance. Rolling loosely in the auricle, it had no connection with surrounding parts. When cut open, after having been kept for some days in diluted alcohol, it was found to consist of a sac, one-eighth of an inch in thickness, formed of an immense number of firm, smooth laminæ, which could be easily separated from each other. Within the cavity formed by this sac was contained a quantity of coagulated blood." Adherent to the wall of the auricle near the mitral valve was a firm, oval thrombus on the free surface of which was a superficial concavity which formed a "kind of socket for the loose ball to roll in." This last feature is a unique observation.

In 1863, Dr. J. W. Ogle reported a typical instance of ball-thrombus in the left auricle with extreme mitral stenosis, and accompanied the report with an admirable drawing. In 1877 Dr. Wickham Legg reported likewise, to the London Pathological Society, two cases of ball-thrombi in the left auricle with mitral stenosis. He refers to Ogle's specimen which he re-examined, and to a fourth specimen in the museum of St. Thomas's Hospital. One of his cases is unique in the presence of two ball-thrombi in the left auricle. This patient was brought dead to the hospital, and presumably died suddenly in the streets. Von Recklinghausen's brief description, in 1883, of two cases of ball-thrombi is quoted in the subsequent German records on the subject as the first observation of this interesting form of cardiac thrombus; although there were much fuller previous accounts of at least four cases, with mention of a fifth, in Scotch and English records extending back as far as 1814; those of Ogle and Legg being certainly very accessible in the *Transactions of the London Pathological Society*. Macleod's case of loose thrombus in the right auricle is properly excluded by von Recklinghausen from the class of ball-thrombi. If the conception of a ball-thrombus be simply that of a loose thrombus too large to pass through

the valvular orifice, then van der Byl's case, reported in 1858, should be included in this class. He found in a case of sudden death "an irregular, shaggy-looking mass sticking" in the extremely contracted mitral orifice. When floated out in water this assumed a sac-like appearance, was about the size of a pigeon's egg, and completed a broken thrombotic sac in the auricular appendix. This embolus must have been freshly detached, and had not assumed the typical spherical or ovoid shape of the ball-thrombus. There have been later reports of ball-thrombi, by Hertz (two cases), Osler (two cases), Arnold, von Ziemssen, Redtenbacher, Krumbholz, Rosenbach, Stange, and Eichhorst (three cases mentioned without any details), making twenty, without including Macleod's and van der Byl's cases.[1] Of these, fifteen are reported with sufficient details for analysis. This form of thrombus, therefore, although rare, is not so much of a curiosity as has been generally supposed.

Three characters, in my opinion, should enter into the definition of a ball-thrombus: (i.) entire absence of attachment and consequent free mobility; (ii.) imprisonment in consequence of excess in the diameter of the thrombus over that of the first narrowing in the circulatory passage ahead of it; and (iii.) such consistence and shape that the thrombus must not of necessity lodge as an embolus in this passage. The third point does not prejudice the question of the possibility of a ball-thrombus lodging as an embolus; but it excludes from the group such detached, shaggy, irregular masses (as in van der Byl's case) as must necessarily be caught at once as emboli in the narrowed passage in front. According to this definition a ball-thrombus might, theoretically at least, occur in any circumscribed or sac-like dilatation of the circulatory system; indeed von Recklinghausen considers loose phleboliths and cardiac ball-thrombi as analogous.

All of the cardiac ball-thrombi—as thus defined—hitherto reported, were in the dilated left auricle; and, with one exception, were associated with mitral stenosis. In Stange's case there was aortic stenosis, with slight insufficiency of the mitral valve without stenosis. The agency of mitral stenosis in the production of ball-thrombi is not only that it prevents the escape of detached thrombi which might pass the normal orifice, but also that it favours the formation of thrombi in the left auricle, particularly in the appendix; and doubtless also, through the particular disturbance of the circulation, aids in their detachment, increases the tendency to their rotary motion, and prevents the complete emptying of the left auricle during systole, thus rendering more difficult the lodgment and fixation in the valvular orifice of thrombotic masses which at first may be irregular in shape.

The thrombi have varied in size from that of a small walnut to that

[1] I have also not included Schmorl's case, mentioned by Stange, as it is evidently identical with that of Krumbholz, nor Fürbringer's case of numerous globular thrombi, the largest the size of a cherry, in the right auricle, although he reports it as belonging to the group of ball-thrombi. He is evidently under a misconception of the nature of ball-thrombi. There was not the slightest reason why these small bodies, many of them indeed minute, if they were really loose during life, should not have travelled on with the blood-stream.

of a hen's egg; in Wood's case the thrombus was over an inch and a half in diameter, and in Ogle's the weight was more than four drachms. In ten the shape was spherical; in four ovoid; in one (probably of recent separation) a somewhat irregular flattened hemisphere. In six the surface was smooth and polished; in six marked by granules, lines, ribs, or little depressions; in two smooth and knobbed; and in one (Redtenbacher's) beset with very fine, gray, fibrinous villi. Nine were centrally softened; four solid throughout; and for two there is no statement on this point. The colour was gray or reddish gray; in Wood's "darkish red." In the majority of cases it is said there were adherent thrombi in the left auricle, usually the appendix; and where this is not expressly stated they may have been present. In five cases only was there a rough or projecting spot on the surface of the ball indicative of the previous attachment; and in two this spot was not at all smoothed off: so that the detachment was evidently very recent, possibly indeed during the autopsy, as in one of the two loose balls in Legg's first case. Krumbholz says that the surface of his thrombus was covered with endothelium. In none, however, was any distinct evidence of organisation detected, for von Ziemssen's statement on this point is too indefinite to be considered.

Ogle, in 1863, clearly recognised the mode of production of a ball-thrombus "by the constant and free agitation of a fragment of fibrinous coagulum separated from some part of the endocardium, and uniformly increased by fresh material at its circumference precipitated from the surrounding blood-stream." Von Recklinghausen has given the fullest and most satisfactory explanation of the spherical shape and smooth surface, in noting that at least some ball-thrombi have a globular shape when first detached; and that irregular bodies, of the consistence of thrombi, rotating in a cavity and growing by successive accretions, assume a spherical shape by a process of moulding, and not by the grinding or breaking off of corners and projections, as was suggested by Hertz to account for the smooth roundness of ball-thrombi. In two or three instances where the ball-thrombus has consisted of a central irregular nucleus enveloped in a concentrically laminated capsule, it has been assumed that the former represents the original detached part, and the latter successive accretions during free rotation in the auricle. While suggestive of such an interpretation, this structure may, however, exist in still adherent globular thrombi. It seems to me probable that most ball-thrombi are smooth and at least approximately spherical when first detached. It is difficult to say how much a thrombus may have grown after its separation.

In nearly all cases the loose thrombus apparently came from the left auricular appendix, where adherent thrombi were rarely missed when it is expressly stated that they were searched for. In Wood's case the dark red colour, central blood-clot, and polished surface suggest the possibility that the loose body was a separated polypus resulting from hæmorrhage in the wall of the auricle or from a varix; and this opinion

is strengthened by the socket-like depression in the adherent thrombus, for it is not clear how such a socket could be formed by a thrombus loose in the auricle; but it might have been the impression left by a polypus attached at some other point.

As regards the clinical significance[1] of cardiac ball-thrombi, Wickham Legg expressed the notion which would probably at first occur to most persons. "A loose thrombus," he says, "in the left auricle would at any time be ready to act as a ball-valve, and stop the circulation in the mitral orifice"; and in this opinion he was strengthened by the presumably sudden death of his patient. Von Recklinghausen, however, who at the time knew only of his own two cases and the two of Hertz, in criticising a similar opinion expressed by the latter, brought forward several arguments opposed to this notion. The main points of his argument are that instances of sudden death are not infrequent in extreme mitral stenosis without ball-thrombi; that lodgment of the thrombus in the mitral orifice has not been observed, and, even if it were found lying loosely over the orifice at the autopsy, that this would not indicate its position at the moment of death; that the funnel of the stenosed mitral orifice is elliptical in cross-section and shallow, so that a rolling sphere of the consistence of a ball-thrombus could neither completely occlude it nor get wedged in it, nor, if the ball should enter the shallow funnel, is there anything to hold it there, so that the next moment it would roll out. To these points may be added Arnold's argument that the thrombus cannot be horizontally pressed by the auricular contractions against the orifice; for during its systole the dilated auricle does not completely empty itself of blood through the stenosed orifice.

The histories of the cases of cardiac ball-thrombus support in general the position of von Recklinghausen. No symptoms were observed which may not occur in mitral stenosis. Death was gradual in all except four. In only one of these four cases of sudden death was there any conclusive evidence that the thrombus was the cause. This was Dr. Osler's second patient upon whom the autopsy was made in my laboratory by Dr. Flexner. The patient, a woman aged 20, was seen in good condition a few hours before death. At 4.30 A.M. she was found by the nurse very cyanotic, she gave a gasp or two, and died in a few moments. At the autopsy were found marked hypertrophy and dilatation of the left auricle, right ventricle, and to a less extent right auricle; without dilatation or hypertrophy of the left ventricle. The segments of the mitral valve were thickened, adherent, and drawn down by great shortening of the chordæ tendineæ, so as to form the wall of a distinct funnel. There were no fresh vegetations and no œdema. The stenosis was not extreme, the mitral orifice readily admitting the index finger. The other valves and the coronary arteries were normal. An ovoid ball-thrombus, resembling a thick chestnut, measuring 4 × 3·5 × 3 ctm., was found, upon

[1] In order to complete without interruption the description of ball-thrombi I introduce here their clinical significance, although the consideration of the symptoms of thrombosis is taken up subsequently.

opening the heart, occupying with its smaller end and completely blocking the funnel-shaped mitral orifice, from which it was readily removed by the fingers. At one pole of the thrombus was an irregular, roughened spot indicating a former attachment, probably to a thrombus in the appendix. There can be no reasonable doubt that the thrombus in this case was the cause of the sudden death, which is certainly not a common occurrence with such moderate uncomplicated mitral stenosis at the age of this patient. Indeed sudden death is less common in uncomplicated mitral stenosis than in aortic valvular disease; as the former occurs often in young women, and is usually unassociated with disease of the coronary arteries. In the three other instances of sudden death with ball-thrombus the ages were 21, 22, and 39 years respectively. Only in one of these was the thrombus a perfect sphere; so that it would appear that an oval thrombus is more likely to plug the mitral orifice than a spherical one. This view is strengthened by the fact that of the four observations of ovoid thrombi in three death was sudden. In the light of our case it seems clear that a ball-thrombus may "act as a ball-valve and stop the circulation in the mitral orifice," as suggested by Legg; but it is certain that this is an exceptional occurrence.

Under the name of cardiac *pedunculated polyps* various formations have been described. Some of these are ordinary unorganised or partly organised polypoid thrombi, about which nothing more need be said; but others are very remarkable structures which occupy an entirely exceptional position, not only among cardiac thrombi but among thrombi in general. In the older records some of the latter were described as fibromatous or myxomatous polyps,—two as hæmatoma; but in the later reports most have been recognised as organised thrombi. They are often called true polyps in distinction from the false polyps of the older writers.

The literature of the subject begins with Allan Burns in 1809. References to many of the cases will be found in the papers of Hertz, zum Busch, and Pawlowski. Among the noteworthy observations since Hertz are those of Czapek, Voelcker, Bostroem, and Ewart and Rolleston. I have found records of thirty-three cases, at least twenty of which were well-characterised, organised, pedunculated polyps. Twenty-five sprang from the wall of the left auricle, usually the septum; four from the right auricle; four from the left ventricle.

The following are the more notable features of these curious formations:—In many instances no cause whatever could be found for their occurrence. The hearts containing them were often otherwise entirely normal, with the exception of changes manifestly secondary to the polyp, such as nodular fibroid thickening of the mitral segments and dilatation and hypertrophy of the left auricle and right ventricle. Unlike other cardiac thrombi they are solitary formations, and often unassociated with ordinary thrombotic deposits. The vast majority of these polyps spring from the septum of the left auricle near the fossa ovalis with short pedicle, sometimes narrow, sometimes broad. They are firm or

gelatinous, elastic, ovoid or pear-shaped formations, in several instances hanging down into the left ventricle with a constriction corresponding to the mitral orifice. The surface is usually glistening, smooth, and covered by a distinct membrane which often resembles the endocardium. It may present calcific, atheromatous, or pigmented patches; and upon it may be irregular knobs and depressions. The colour is described as yellowish, gray, dark red or brownish red; the colour often varying in different parts of the polyp. A prevailing dark red colour has been observed in a large number of the cases. In distinction from nearly all other cardiac thrombi, these polyps are more or less organised by connective tissue and vessels; the organisation in some being little marked, in others so far advanced that the structure resembles that of a fibroma or myxoma. The central part is often unorganised or less organised than the base and periphery. In the incompletely organised forms the substance of the polyp is composed of red corpuscles, fibrin, granular detritus, yellow blood-pigment, leucocytes, and other cells between the blood-vessels and fibrous septa. Laminated fibrin may be present in the peripheral layers. Unless ordinary thrombi are likewise present, emboli are usually missed. A further distinction from the ordinary cardiac thrombi is that many of these polyps, by encroaching upon the mitral orifice, are of as much clinical as anatomical interest; the diagnosis during life in these cases being mitral disease, usually stenosis.

We have no satisfactory explanation of these pedunculated polyps. The ordinary causes of thrombosis are generally absent. Their commonest site of origin, the septum of the left auricle near the oval fossa, is not a usual situation for ordinary thrombi. They stand in no demonstrable relation to patency of the foramen ovale or to circumscribed endocarditis in this situation.

Bostroem has suggested that an explanation may be found in the existence of varicose veins which have been observed repeatedly in the septum, usually near the posterior quadrant of the foramen ovale. A difficulty with this explanation is that nine out of ten of the varicosities observed by Wagner, Zahn, Rindfleisch, and Bostroem were on the right side of the septum. In one instance, however, Bostroem found in the left auricle a spherical, dark red polyp, 13 mm. in diameter, attached by a short narrow stem to the septum on the posterior lower margin of the completely closed foramen ovale. This proved to be a varix containing a phlebolith. In another case a similar thrombosed varix had broken from its pedicle on the septum of the right auricle, and was lodged as an embolus in a branch of the pulmonary artery. He suggests this as a possible source of ball-thrombi. Of still greater significance is Bostroem's demonstration in an old museum specimen, labelled "thrombosis of the right auricle (pedunculated cardiac polyp) peripherally organised," of an enormous completely thrombosed varix almost filling the right auricle. In still another case he proved conclusively that a broad-based, nearly spherical polyp, occupying a large part of the right auricle, was a hæmorrhage in the wall of the auricle. Choisy and

Nuhn long ago interpreted the polyps, which they observed, as the result of hæmorrhage in the septum of the left auricle.

In the light of Bostroem's interesting investigations, more attention than has been customary should be given to the possibility that pedunculated polyps are the result of hæmorrhage or are thrombosed varices. Most competent investigators, however, have unhesitatingly pronounced the polyps which they have examined to be organised thrombi. It would appear, therefore, that the nature of these formations is not always the same. At any rate the great majority of the typical pedunculated polyps, to which the preceding description applies, occupy a position quite apart from ordinary cardiac thrombi. As already remarked, by no means all of the cases described as true cardiac polyps belong to this peculiar group. Some, as in Krumm's case, are ordinary partly organised thrombi attached to diseased patches of the heart wall.

Association with Certain Diseases.—Thromboses may be divided, as regards their clinical relations, into the following groups: (i.) those resulting from direct injury of vessels, including the penetration of foreign bodies; (ii.) referable to diseases of the vascular wall, as to angio-sclerosis, syphilitic arteritis, aneurysm, varix; (iii.) caused by lesions of neighbouring parts; (iv.) thromboses of arteries and veins whose terminal branches end in septic and gangrenous areas; (v.) complications or sequels of (*a*) infective diseases, (*b*) cachectic and anæmic states, (*c*) cardiac disease, (*d*) certain constitutional diseases; (vi.) idiopathic and primary infective thromboses. Several of these groups, being mainly of surgical interest, will not be considered here. The thromboses embraced in the fifth and sixth groups are of such special medical interest that it is proper in this article to give them particular attention; although it is manifestly impossible within reasonable limits to take up all in detail. Some of them are noticed in other parts of this work.

Enteric fever.—Cardiac thrombosis is a rare complication of enteric fever. In 2000 fatal cases of enteric fever in Munich there were only eleven instances of acute endocarditis (Hölscher). Girode, Viti, Carbone, and Vincent have found the typhoid bacillus in endocardial vegetations; and vegetative endocarditis has been produced experimentally by intravascular injections of pure cultures of the typhoid organism combined with injury to the valves. More frequently the endocarditis has been due to secondary infection. In rare instances in the course of enteric fever globular thrombi are formed in the auricular appendages and ventricular apices; and these, as well as the endocardial vegetations, may be the source of emboli.

Arterial thrombosis is a still rarer event, but, in consequence of its gravity, an important one. Bettke, in 1420 cases, found four of gangrene of the extremities; but in 2000 Munich autopsies no instance is recorded, a result in contrast with fifty-nine of thrombosis of the femoral vein in the same series. Keen, in his admirable monograph, has collected and analysed 115 cases of gangrene associated with enteric fever, and due to plugging of the arteries. In twenty-one cases arterial thrombosis was

observed without gangrene, the absence of which is much more common with thrombosis of arteries of the upper extremity than of the lower. The earliest appearance of the gangrene was on the fourteenth day; the latest in the seventh week. In the great majority of cases the thrombus was seated in the arteries of the extremities; and in those of the lower far more frequently than of the upper. In eight out of eleven cases of arterial thrombosis of the lower extremities, collected by Barié, the posterior tibial artery was concerned. In contrast with venous thrombosis the right side is the seat as often as the left.

Other arteries, as the pulmonary, the superior mesenteric, and the cerebral, may become thrombosed. Four fatal cases of typhoidal thrombosis of the middle cerebral artery, or its branches, have been reported (Huguenin, Barberet and Chouet, Vulpian and Osler); and other cases have been recorded in which the diagnosis of cerebral thrombosis was made from the symptoms. In Osler's case, in which Dr. Flexner and I examined the brain, the middle cerebral artery was open; but the ascending parietal and parieto-temporal arteries and their branches were occluded by adherent, firm, mixed thrombi. The adjacent brain substance was studded with punctiform hæmorrhages, but not much softened. Typhoid bacilli were widely distributed in the body.

The arterial thrombosis may be secondary to embolism; but in the great majority of cases it has been reported as autochthonous. In the older records the thrombosis has been usually regarded as marantic; whereas the tendency now is to refer it to an infective arteritis; a view which is probable, although we have few conclusive observations in its support. Rattone and Haushalter claim to have demonstrated the typhoid bacillus in the walls of occluded arteries; and Gilbert and Lion, Crocq, and Boinet and Ramary have produced an acute aortitis experimentally, by injuring the vessel wall and then injecting typhoid bacilli into the circulation. The bacteriological studies are too meagre and unsatisfactory to warrant any definite statements as to the specific cause of arterial thrombosis in enteric fever.

The far commoner venous thrombosis of enteric fever has been adequately considered by Professor Dreschfeld in vol. i. p. 817; and the points bearing on its causation have been presented under Etiology. Richardson has called special attention to the "marantic" thromboses of intracranial veins complicating enteric fever.

Influenza.—Nearly all of our knowledge of thrombosis in influenza dates from the pandemic of 1889-90, which led to the recognition of countless complications, among which those of the circulatory system occupy a less prominent place than the respiratory and nervous. *Arterial thrombosis*, although far from common, is still not an extraordinarily rare complication or sequel of influenza. It is more common in this disease than in any other acute infection. In a few instances it appeared as early as the third to the fifth day, but in most during convalescence. Over forty cases of arterial thrombosis or of gangrene accompanying or following influenza have been reported. References to many

of these will be found in the monographs of Leichtenstern and of Lasker; but their lists are far from complete. In a partial collection of the cases I find that the poplitcal artery was occluded in six; the femoral in four; the iliacs, the axillary, the brachial, the pulmonary, and the renal each in two; and the central artery of the retina (embolism being probably excluded) in one. The cerebral arteries were repeatedly invaded. In several instances there were multiple thrombi. Symmetrical gangrene following bilateral plugging was observed in a number of cases. Gangrene was observed in all the cases of occlusion of the arteries of the lower extremities, but not regularly with that of the upper.

It is difficult to say in how many cases the occlusion was due to embolism. Endocarditis is a rare but recognised complication of influenza, and globular cardiac thrombi have also been observed. In the great majority of cases it seems clear that there was primary arterial thrombosis.

Venous thrombosis is a far commoner result of influenza; and has been the subject of a special memoir by Chaudet, and of numerous articles in the medical journals of all countries. Twenty-five cases are recorded in Guttmann and Leyden's collective investigation, and many additional ones are to be found in the vast literature on influenza. Dr. Goodhart, in his article on "Influenza" (vol. i. p. 683), notes the frequency and the occasional diagnostic value of this complication, which may appear during the course of the disease or weeks afterwards, and in mild as well as severe cases. In the great majority of instances the femoral vein was attacked; but the veins of the upper extremity were thrombosed more frequently than in other acute infective diseases. Leichtenstern notes the acute onset and course in some of the cases. There are records of thrombosis of the cerebral sinuses in influenza. Klebs and Kuskow describe capillary thrombi in the lungs.

Few observers are satisfied with the explanation of either the arterial or the venous thromboses of influenza as marantic. Leyden suggests as a cause increase of blood-platelets from disintegration of leucocytes. Evidences of such disintegration, or of masses of platelets in the blood, have been noted by Klebs, Chiari, and Bäumler. Maragliano observed the onset of necrobiotic changes of the red corpuscles in influenza almost immediately after withdrawal of the blood. French writers for the most part attribute the thrombosis to infective arteritis or phlebitis (artérite grippale, phlébite grippale). Rendu, however, in his case of arterial thrombosis rejects this explanation; as he found the walls of the thrombosed arteries entirely normal (nothing is said of a microscopical examination), and he attributes the thrombosis to feeble circulation. In his case there was also a thrombus with softened centre in the left ventricle, and the occlusion of the artery may have been due primarily to an embolus. Gerhardt attributes the gangrene in his case to spasm of the arteries, considering it therefore analogous to symmetrical or arterio-spastic gangrene. In support of the more probable view that the thrombosis is the result of some change in the vascular

wall, directly referable to infection or intoxication, Kuskow observed with great frequency degeneration, proliferation, and desquamation of the vascular endothelium in influenza. In a fatal case of influenzal phlegmasia alba dolens Laveran found streptococci in the blood. These organisms have often been found in the blood and organs of those dead of influenza.

In a remarkable case of multiple thrombotic vegetations present in large numbers in the pulmonary artery, especially in the left main branch, and also on the pulmonary valves (other valves normal), Flexner in my laboratory found in the thrombus, chiefly enclosed within polynuclear leucocytes, very numerous, extremely delicate bacilli, which were identified as the influenzal bacilli of Pfeiffer. This establishes the occurrence of an acute arteritis and thrombosis due to the bacillus of influenza.

Pneumonia.—The sixteenth century error of mistaking for ante-mortem coagula the firm, yellowish white cardiac clots, intimately intertwined with the columnæ carneæ, and found after death from pneumonia more frequently than from any other disease, has not wholly disappeared at the end of the nineteenth century; for coagulation of blood in the right heart is still occasionally spoken of as a special danger in pneumonia. Genuine ante-mortem thrombi in the cavities of the heart occur in pneumonia, but they are rare; being much less common than in many diseases in which death from "heart-clot" is not mentioned as a special danger. Acute valvular endocarditis is a well-recognised complication of pneumonia. Mention has already been made of coagula in pulmonary vessels directly connected with the inflamed lung (p. 160).

Benedikt, Brunon, Rendu, Leyden, and Blagden have observed gangrene of the extremities consecutive to arterial thrombosis in pneumonia. Blagden's patient was a woman 92 years old. In Leyden's case there was thrombosis of the lower end of the abdominal aorta. Gangrene of the extremities in pneumonia may also be the result of embolism; of this event Osler has observed an instance.

Venous thrombosis, although more frequent than arterial, is scarcely mentioned in text-books as a complication or sequel of pneumonia. Few cases have been reported. Da Costa, in a valuable article on the subject, reports three personal observations, and has collected from the literature six additional ones, and two which are doubtful. In addition to these, I have found reports of cases by Barbanceys (two cases), Lépine, Fabrès, Valette, Mya (two cases), and Lee Dickinson (seven cases), making a total of twenty-three cases of venous thrombosis in pneumonia. The femoral or internal saphenous veins were those invaded, the affection being oftener on the left than on the right side. There were at least three deaths from pulmonary embolism consecutive to the thrombosis. The affection, if one may draw any conclusion from so small a number of cases, is more common in women than in men. Of 367 cases of pneumonia, observed by Dickinson, peripheral venous thrombosis occurred in seven, of which four were in young women, two of these being chlorotic. In

several instances of influenzal thrombosis pneumonia had occurred. Laache ranks pneumonia next to influenza and enteric fever as regards the frequency of occurrence of peripheral thrombosis; but this event is far commoner in the last two diseases. The affection occurs during convalescence, rather than in the course of pneumonia; and presents the same general characters as the phlegmasia alba dolens of enteric fever. Da Costa very plausibly attributes it to a primary infective phlebitis. Mya, in one of his cases, found pneumococci in large numbers in the thrombus.

Acute articular rheumatism.—There was a time when rheumatic phlebitis ranked in importance next to the puerperal form; but it is now recognised that most of the cases of thrombosis attributed by the older writers to rheumatism had nothing to do with acute articular rheumatism. Schmitt and Vaquez have sifted the reported cases, and they find that, while phlebitis or venous thrombosis is to be recognised as a complication of genuine acute rheumatism, it is a rare one. The infrequency of this event is noteworthy in view of the fibrinous state of the blood and the frequency of acute endocarditis. Gatay has reported a doubtful case with negative result of the bacteriological examination of the thrombus. Legroux reports an instance of thrombosis of the brachial artery without gangrene in acute articular rheumatism.

Appendicitis.—Mention may be made of the occurrence of thrombosis with appendicitis, as this affection is of medical as well as surgical interest. Besides the septic thrombo-phlebitis of the mesenteric and portal veins, thrombosis of the iliac and femoral veins may occur on the left side as well as on the right. The published reports indicate that this is more common on the right side; but in the 131 cases of appendicitis in the service of my colleague Professor Halsted, with the notes of which Dr. Bloodgood has furnished me, there were four instances of peripheral venous thrombosis, all of the left leg; one being limited to the calf. Three of these were in chronic appendicitis, the operation being between the attacks. Mynter, who has also observed thrombosis of the left femoral vein, attributes it to great prostration and weak circulation. It is interesting to note the analogy of appendicitic thromboses to puerperal thromboses, where we also have septic and suppurative thrombi in veins immediately adjacent to the inflamed organ, and less manifestly infective thrombi in the veins of the lower extremities. It is probable, however, that the latter thrombi in appendicitis, as well as in the puerperal cases, are frequently caused by bacteria, and oftenest by streptococci, which are concerned in both affections with great frequency. In one of Mynter's cases sudden death was probably due to pulmonary embolism following thrombosis of the femoral vein.

Other acute infective diseases.—It would lead too far to continue a detailed inquiry into the association of thrombosis with other acute infective diseases. It must suffice to specify typhus fever, relapsing fever, dysentery, erysipelas, suppurative tonsillitis, diphtheria, variola, scarlatina, measles, Asiatic cholera. In many instances thrombosis,

as associated with specific infective diseases, has been due to a secondary septicæmia, streptococci being the commonest secondary invaders. The disposition in or after typhus fever to arterial as well as to venous thrombosis should be especially emphasised. Thrombosis has been added to the growing list of complications of gonorrhœa (Martel, Perrin, and Monteux and Lop).

Tuberculosis.—The consideration of thrombosis directly referable to tuberculous processes adjacent to vessels need not detain us. The occurrence of intimal tubercles, where the evidence is conclusive that tubercle bacilli have penetrated the inner lining of vessels directly from the circulation in the main channel, may be mentioned not only as a cause of thrombosis, but also as an interesting illustration of this mode of infection of the vascular wall. Several instances of endocarditis caused by the tubercle bacillus have been described, and mention has already been made of tuberculous cardiac thrombi (p. 184). Michaelis and Blum have produced vegetative tuberculous endocarditis experimentally, by injuring the valves in rabbits and then injecting tubercle bacilli into the ear veins. Particularly demonstrative of infection taking place through the vascular endothelium are the rare instances of tuberculous foci in the aortic intima, without invasion of the outer coats, and without tuberculosis of neighbouring parts. Two instances of this form of aortic tuberculosis have been observed in my laboratory, and described by Flexner and Blumer. I have recently examined a section, in the possession of Dr. Gaylord, of a superficial tuberculous focus in the intima of the aorta with an exquisite platelet and fibrinous thrombus containing tubercle bacilli attached to the nodule. A similar case has been described by Stroebe. These rare instances are cited because they furnish conclusive proof that bacteria may penetrate the inner lining of vessels from the main channel, even where the blood-current is forcible; and may set up inflammation of the intima with secondary thrombosis. Hektoen's interesting observations of changes in the intima of vessels in tuberculous meningitis furnish additional evidence along the same lines.

Arterial thrombosis, outside of the forms to which reference has just been made, and which are of pathological rather than clinical interest, is a rare event in tuberculosis. Most common are the instances of thrombosis of the pulmonary artery or its main branches in phthisis. Dodwell mentions an instance of thrombosis of both popliteal artery and vein. Vaquez, in chronic pulmonary tuberculosis, describes an interesting case of thrombosis of the left subclavian, axillary and brachial arteries with gangrene of the arm: he found streptococci in the plug and in the wall of the vessel, including the vasa vasorum, but no tubercle bacilli.

On the other hand, peripheral venous thrombosis in advanced phthisis is a comparatively common and well-recognised ailment. In the great majority of cases veins of the lower extremities, the left oftener than the right, have been plugged; but the thrombus may be in

the inferior vena cava, or other veins, or the cerebral sinuses. Dodwell, in his valuable paper on this subject, places the proportion of cases of phthisis with this complication at about 3 per cent. In about 1300 necropsies of phthisical patients at the Brompton Hospital there were twenty cases of thrombosis of veins of the lower extremities (1·5 per cent).

The peripheral venous thromboses of advanced phthisis are usually cited as typical examples of the marantic or cachectic form. Dodwell, however, while recognising enfeebled circulation as a factor, is inclined to refer the thrombosis to some unknown change in the vascular wall set up by a complicating septicæmia. He emphasises the infrequency of venous thrombosis with the acute and the very chronic forms of phthisis, and its relative frequency with an intermediate type with remittent or continued fever. He also noted association with intestinal and laryngeal ulceration in a larger percentage of the thrombotic cases than the average. As is well known, secondary septicæmias, usually streptococcal, are very common in phthisis.

There are several records of bacteriological examination of the peripheral thrombi in phthisis, which show that they may be of mycotic origin. Vaquez found tubercle bacilli, without other micro-organisms, in a thrombus of the left profunda and femoral veins. They were present also in the wall immediately beneath the endothelium, but were absent from the media and adventitia. Sabrazes and Mongour in two instances found tubercle bacilli both in the plug and in the wall of a thrombosed iliac vein: they were associated with micrococci. More frequently micrococci, presumably pyogenetic, have been found, without tubercle bacilli, in the thrombi and vascular walls: examples of this are recorded by Vaquez. Notwithstanding these suggestive bacteriological findings it would be quite premature to conclude that all the peripheral venous thromboses of phthisis are referable to direct infection of the venous wall by bacteria. In a rather old thrombus of the iliac and femoral veins in phthisis I failed to find any micro-organisms, either by culture or by microscopical examination.

Hirtz has called attention to the occurrence of phlebitis in the initial stage of phthisis. Some cases so reported have appeared to be chlorotic in origin.

Cachectic states.—Of other marasmic or cachectic states, in which thrombosis is somewhat frequent, may be especially mentioned those resulting from cancer, dysentery, chronic diarrhœa, gastric dilatation, prolonged suppurations especially of bone, anæmia from loss of blood, and syphilis. The association of thrombosis with syphilis has been recently discussed by Barbe. Phthisis has just been considered. It is especially in the young and the very old that these conditions are most likely to produce thrombosis. Thromboses of the cerebral sinuses, and of the renal and other veins, in marasmic infants, particularly after diarrhœa, are well recognised. Peripheral venous thrombosis is more often associated with the waxy kidney than with other forms of Bright's

disease. The thrombi occasionally found in the renal veins in chronic diffuse nephritis are probably due to local causes, and not to cachexia.

There is a French thesis by Rigollet on thrombosis in malaria, and Pitres, Bitot, and Regnier have likewise called attention to the subject. It is doubtful whether there is any relation between malaria and thrombosis. In over 2000 cases of malaria observed in Professor Osler's service at the Johns Hopkins Hospital no instance of thrombosis was found. (Personal communication by Dr. Thayer.)

Trousseau attached some diagnostic significance to the occurrence of thrombosis in cancer. There have been instances of latent cancer of the stomach in which peripheral venous thrombosis was the first symptom to attract attention, as indeed it was in Trousseau himself who died of gastric cancer. Gouget has reported a case of widespread venous thrombosis, of eight months' duration, which was the only affection observed during life. At the autopsy a small cancer of the stomach was found. Dr. Osler has told me of a personal observation of very extensive multiple thrombosis associated with cancer of the stomach.

The principal seats of cachectic thromboses are the auricular appendages, between the columnæ carneæ of the right heart, in the veins of the lower extremities, the cerebral sinuses, the pelvic veins, and the renal veins. Lancereaux has strongly urged that this form of thrombosis never occurs in the arteries. Doubtless in not a few reported cases embolism has not been satisfactorily excluded; but older observations of Charcot and von Recklinghausen, and several recent ones, leave no doubt of the occurrence of genuine so-called marantic or cachectic thrombi in arteries, even in the aorta.

While pre-existing vascular disease, particularly angio-sclerosis and varicose veins, are predisposing conditions, these plugs are often seated upon intimæ which show very slight alteration. Indeed competent observers have repeatedly described the vessel wall beneath marantic thrombi as normal. While secondary septic infections often participate in the causation of cachectic thromboses, the view that all have this origin is at present unsubstantiated. It is clear that enfeebled circulation is of importance in their causation; but, for reasons already stated, there must be some additional element, which, in many cases at least, cannot well be other than changes in the composition of the blood. The nature of these changes is not known. Possibly increase of platelets, or a special vulnerability of cells, perhaps of the red corpuscles from which platelets are derived, may be concerned.

Cardiac incompetency.—I have already had occasion in this article to speak repeatedly of the importance of feebleness of the general circulation in the causation of thrombosis. Thrombi in the heart itself have been considered (p. 182). In this respect attention is called to the occurrence of peripheral venous thrombosis in chronic passive congestion due to cardiac incompetency, chiefly from valvular disease. Especially noteworthy, in view of the slow venous circulation and the frequency

of cardiac thrombi in this condition, is the infrequency of peripheral thrombosis. Hanot and Kahn, in reporting an instance of thrombosis of the right subclavian vein, say that they were able to find in the French literature, which is exceptionally rich in clinical contributions to the subject of thrombosis and phlebitis, only five additional observations of peripheral venous thrombosis in cardiac disease. I do not think that this complication is quite so rare as would appear from this statement; for, without any systematic effort to collect cases, I have found records of eighteen additional ones—Ramirez (two cases), Baldwin, Nicolle, Hirschlaff (two cases), Robert, Ormerod, Mader, Huchard (two cases), Cohn (three cases), Cheadle and Lees (three cases reported by Poynton); and I have observed two instances of femoral and iliac thrombosis associated with mitral regurgitation.

The most notable fact concerning these twenty-six cases is that seventeen were thromboses of veins of the neck or upper extremity or both, far more frequently of the left than the right side; and one of the innominate veins. In one of Cheadle and Lees' cases the innominate, subclavian, axillary, and internal and external jugular veins upon both sides, the left inferior thyroid, and the upper two-thirds of the superior vena cava were thrombosed; and in another of their cases both internal jugulars and both innominates were completely plugged, and there was a mural thrombus in the upper part of the superior vena cava. It may be that femoral thrombosis is more common in heart disease than would appear from these figures; it is less likely to be reported than thrombosis of the neck and arms, and, on account of the œdema attributable to cardiac insufficiency, may more readily be overlooked both at the bedside and the autopsy table. When, however, we consider that Bouchut places the ratio of thromboses of the upper extremity to those of the lower at 1 to 50, the relatively large number of the former associated with cardiac disease is certainly most striking. The clinical histories seem to show that thrombosis is more likely to occur in the cases with tricuspid regurgitation than in others; but it is certainly even then a very rare event. In several cases there was some complication, especially pressure on the veins and tuberculosis. The explanation of the greater frequency of the thrombosis on the left than the right side has already been given (p. 181).

The relative freedom from peripheral venous thrombosis in cardiac disease, in spite of conditions of the circulation apparently favourable to such an occurrence, may perhaps be attributable partly to the reduction in platelets in this condition (which has been noted by van Emden), and partly to the absence of von Recklinghausen's "Wirbelbewegung" (p. 181), an irregularity of the circulation which occurs especially in vessels too wide in proportion to the amount of blood which they receive. Hanot and Kahn refer the thrombosis to a cachectic state developing in the last stages of cardiac disease. Huchard likewise attributes it to cardiac cachexia associated with secondary infection. Cheadle and Lees' three cases are referred by Poynton, who

reports them, to rheumatic infection. The bacteriological examination was negative.

As will appear later (p. 275), there is evidence that arterial plugging associated with mitral stenosis is due oftener to primary thrombosis than is generally supposed.

Chlorosis.—The association of thrombosis with chlorosis is of peculiar interest. Professor Allbutt, in his article on "Chlorosis" (vol. v. p. 508), has sketched the more essential features, but has referred some points for consideration here. In the older literature there are reports of plugging of the veins in young women which undoubtedly pertain to chlorosis. Thus William Sankey, in 1814, says: "I have met with two cases in young women, not after parturition; both were severe and well marked; both had obstructed menses." But Trousseau, with his pupil Werner, in 1860 was the first to draw distinct attention to this association. References to the more important records, up to 1898, will be found in the recent article by Schweitzer, from Eichhorst's clinic.

Although thrombosis is not a common complication of chlorosis, it is sufficiently frequent to indicate a special tendency to its occurrence in this disease; a tendency calculated to arrest attention on account of the age and the class of the patients, the obscure causation, and the unexpected and calamitous termination which it may bring to a disease ordinarily involving no danger to life. Some idea of the frequency of chlorotic thrombosis is perhaps afforded by the statements that von Noorden observed 5 instances in 230 chlorotics, and Eichhorst 4 in 243. The list of reported cases was brought by Proby in 1889 to 21, by Bourdillon in 1892 to 32, and by Schweitzer in 1898 to 51. I have found reports of 30 additional cases not included in these lists, and am indebted to Dr. W. S. Thayer for an unpublished personal observation; making a total of 82. (References will be found at the end of this article.) I have also seen 12 other cases mentioned, but without sufficient detail for statistical analysis; and I have come across several references to articles on the subject not accessible to me. Slavic and Italian literature has not been searched, and the American to only a small extent. I have no doubt that mention or reports of over 100 cases of thrombosis chlorotica could be gathered by thorough overhauling of medical books and periodicals. Thirty-one of my cases are from French literature, twenty-five German, eighteen English, three Scandinavian, two American, and one Italian. It would, however, be quite unwarrantable from this literary inequality to infer any difference in the incidence of the affection according to race or country.

The statistical study of these eighty-two cases brings out a number of interesting points, of which some only are directly pertinent to this article. Thrombi in the heart are very rarely mentioned in the post-mortem reports. There were only four instances of primary arterial thrombosis, two being of the middle cerebral arteries (Vergely); one of the pulmonary (Rendu) without thrombosis elsewhere, and one of the right axillary (Tuckwell) with gangrene of the hand and recovery.

Dr. Tuckwell reports his case as one of embolism; but it is usually included among the arterial thromboses, and probably with as much or as little right as the others.

All the remaining 78 cases were venous thromboses. There was thrombosis of the cerebral sinuses in 32 cases (39 per cent), 6 (19 per cent) of these being associated with thrombosis of the lower extremities. In four instances thrombi extended from the sinuses into the internal jugular veins. Unquestionably sinus-thrombosis is represented by too high percentage figures in my list, for the obvious reason that reports of an affection of such gravity and such interest, especially to neurologists, are much more likely to get into print than those of ordinary femoral thrombosis. Still the figures are impressive, and indicate that sinus-thrombosis is not of great rarity in chlorosis; to which malady a leading place among the causes of spontaneous thrombosis of the cerebral veins and sinuses in women must be conceded.

In 51 of the 82 cases there was venous thrombosis of the extremities (62·2 per cent—too low a percentage as already explained); 50 being of the lower and three of the upper, of which only one was limited to the upper extremity. Of the 50 cases of thrombosis of the lower extremities (which are probably involved in at least 80 per cent of all chlorotic thromboses), the process was bilateral in 46 per cent, and unilateral in 54 per cent—34 per cent being left-sided and 20 per cent right-sided. The usual preference of femoral thrombosis for the left side is shown by the beginning of the affection in the left leg in 64 per cent of the thromboses of the lower extremities, in the right leg in 29 per cent, and on both sides simultaneously in 7 per cent. There is in the list one case (Kockel's) with meagre history, in which no mention is made of thrombi outside of the upper part of the inferior vena cava; death ensued from pulmonary embolism. This I have not included among the thromboses of the extremities.

So large a proportion of thromboses involving both lower extremities merits emphasis as a characteristic of chlorotic thrombosis. So again the repeated observations of multiple and successive thromboses, relapses and recurrent attacks (it may be after weeks or after years), all point to the peculiar and widespread tendency to thrombosis in some cases of chlorosis. The most remarkable example of this is Huels' case, in which various large veins of the extremities, trunk and neck became thrombosed in quick succession, until finally only the jugular and right subclavian veins remained free. The patient recovered. In five cases examined after death the inferior vena cava was plugged; and in a few of those who recovered the symptoms indicated extension of the thrombus from the iliacs into this vein.

While the prognosis of chlorotic sinus-thrombosis is extremely bad, Bristowe and Buzzard each report an instance of recovery. Such a possibility has been questioned, but I see no reason to doubt it. Not very infrequently after death in one or more of the intracranial

sinuses thrombi are found which had occasioned no recognisable symptoms during life, and no lesions of the brain.

A fatal issue of uncomplicated thrombosis of the extremities is due almost always to pulmonary embolism, which occurs oftenest in the second to the fourth week after the onset, and usually after some movement of the body. In my collection of cases there are thirteen instances of pulmonary embolism (25 per cent of the fifty-two cases with venous thrombosis outside of the cerebral sinuses). All but two terminated fatally. In some other cases there were symptoms suggestive of embolism; and doubtless emboli lodged in smaller pulmonary arteries without giving any indication of their presence. After making due allowance for the undoubtedly disproportionate representation of embolism of the large pulmonary arteries in published records, this catastrophe remains sufficiently frequent to impart a certain gravity to the prognosis even of simple femoral thrombosis in chlorosis.

There are almost as many hypotheses of chlorotic thrombosis as of chlorosis itself. None of these introduces any factors which have not been considered already under etiology. The principal causes which have been assigned, either singly or in combination, may be grouped as follows: (i.) feeble circulation due to weakness of the heart, sometimes intensified by congenital hypoplasia of the blood-vessels (Virchow); (ii.) alteration of the vascular endothelium, especially fatty degeneration (Eichhorst, Renaut); (iii.) primary phlebitis of unknown causation (Vaquez); (iv.) increase of platelets (Hanot and Mathieu, Buttersack); (v.) some fault in the composition of the blood, variously defined as lowered specific gravity, deficiency of salts (?) (Renaut), presence of extractives derived from muscular activity (Proby), increase of fibrinferment (Birch-Hirschfeld); (vi.) secondary infection (Villard, Rendu, Oettinger, von Noorden).

It is not necessary here to discuss all these views in detail. The data for estimating their value have for the most part already been presented in this article. Such primary lesions of the vascular wall as have been noted in the thrombosed veins have usually been trivial, and are common enough without thrombosis. There is at present no bacteriological basis for the infective supposition. Villard's much-quoted observation is unconvincing; in his case a small piece of a peripheral thrombosed vein was excised and examined by Nepveu for micro-organisms with negative result. Villard adds that Bossano found micro-organisms in the blood, but gives no details; and there is no evidence that these micro-organisms may not have come from the skin. Perhaps more weight should be attached to a few observations in which some source of infection, such as furuncle, was present. Proby, Löwenberg, von Noorden, and other observers have examined the thrombi and blood of chlorotics without finding any micro-organisms. Nevertheless von Noorden and others are favourably disposed to the infective hypothesis, on clinical grounds. Sometimes the onset of chlorotic thrombosis is ushered in by a chill or chilly sensations; usually there is fever, which

may be well marked; and in general the symptoms are thought by some to indicate infection. It does not seem to me imperative to interpret these symptoms as necessarily indicative of infection by micro-organisms.

There are difficulties with all of the hypotheses which have been suggested. I think that there may be some significance for the etiology of chlorotic thrombosis in the increase of platelets noted by Hanot and Mathieu, and by Hayem; and determined more accurately by Muir.[1] I shall also venture to suggest that there may be some nutritive disturbance of the red corpuscles, in consequence of which they disintegrate more readily from slight causes, and produce the granular material, chiefly platelets, which constitutes the beginning white thrombus; and in support of this opinion I will call attention to Maragliano and Castellino's observations of the lowered resistance of chlorotic red corpuscles. Another element which may enter into the causation is some little understood irregularity of the circulation, other than retarded flow, which is manifested in the venous thrills and hums; and which may in certain situations, where thrombi most frequently form (sinuses, femoral vein), lead to the eddies shown by von Recklinghausen to be of importance in the causation of thrombosis; although I confess that the fulness of the veins in chlorosis does not support this suggestion.

Gout.—Since the publication of the classical paper on gouty phlebitis by Paget in 1866, followed by those of Prescott Hewett and Tuckwell, this affection has been well recognised (see art. on "Gout," vol. iv. p. 161). Its causation is unknown. Paget with much reason regards the ailment as a primary phlebitis with secondary thrombosis; and in this he has been followed by most writers on the subject. Although deposition of urates has been found in the sheaths of veins, there is no evidence that gouty phlebitis is caused in this way. Sir W. Roberts, on p. 172 of the article just quoted, ingeniously suggests that the presence of scattered crystals of sodium biurate in the blood may constitute foci around which thrombi may be formed.

Idiopathic thrombosis.—Paget says that the occurrence of phlebitis in elderly persons without any evident external cause warrants the suspicion of gout; and that this is perhaps the most common form of idiopathic phlebitis. There remain, however, rare instances of apparently spontaneous thrombo-phlebitis, occurring in previously healthy individuals, which cannot be explained in this way. Daguillon has observed and collected a number of such cases.

Primary infective thrombosis.—There are rare instances of arterial and venous thrombosis, generally widespread, which present the characters of an acute infective disease without anatomical lesions other than the

[1] Buttersack has recently described the presence in the blood of chlorotics of cylindrical masses of platelets identical with the first form of Litten's blood-cylinders. These he considers to be capillary platelet-thrombi, which have been washed out by the circulating blood. While they may occur in other conditions, Buttersack associates them especially with chlorosis. It remains to be determined whether this cast-like arrangement of platelets is not the result of the mode of preparation of the specimen of blood.

thrombo-phlebitis, or thrombo-arteritis, and the changes consecutive to the vascular obstruction and to the vascular or general infection. The thrombosis may be referable to a primary infective angeiitis, or to a general infection with changes in the blood and circulatory disturbances. The former class of cases may be considered analogous to mycotic endocarditis, the localisation being in the vascular intima instead of in the endocardium. In the latter group, which probably is not strictly separable from the former, the veins or the arteries are plugged with thrombi, which are often extensive and multiple. The venous is more common than the arterial form. Vessels both of the extremities and of the viscera may be invaded. The affection appears as an acute infective fever with the special localisation of the process in the blood-vessels.

As belonging to the group of primary infective thrombo-phlebitides I should interpret a case reported by Dowse. A woman, 43 years old, previously in good health, was suddenly seized with chills, fever, and great prostration, accompanied by the rapid onset of severe pain and œdematous swelling of the right leg. Death occurred after two and a half weeks. At the autopsy the iliac, femoral, popliteal, and deeper veins were found to be filled with mixed, adherent, predominantly red thrombus. The tissues around the thrombosed vessels were suffused with blood.

Osler has reported an instance of the arterial form of primary infective thrombosis. A man, aged 20, who had recovered from typhoid fever two years previously, presented fever, rapid pulse, diarrhœa, and abdominal pain, followed by gangrene of both legs extending to the middle of the thighs. He died about two weeks from the beginning of the illness. At the autopsy was found thrombosis of the femoral and iliac arteries, of the lower two inches of the abdominal aorta, and of two large branches of the splenic artery. The spleen was enlarged, and contained large infarcts, one the size of an orange, which had given rise to peritonitis. There were infarcts also in the right kidney. Numerous micrococci were found in the splenic infarct, and in the exudate covering it. The heart, the intestine, the brain, and the lungs showed no lesions.

Effects and Symptoms.—The lesions and the symptoms produced by thrombi are referable to the obstruction of the circulation caused by the plug, and to the local and constitutional effects of irritative or toxic substances which may be present in the thrombus or vascular wall. It is obvious that these effects must vary with the functional importance of the part supplied by the obstructed vessel; with the rapidity, extent, and completeness of the obstruction; with the location of the plug in heart, artery, capillary, or vein; with the size of the vessel; with the readiness of establishment of a collateral circulation; with the nature of the thrombus, and with associated local and general morbid conditions. Thus the obstruction of each important vessel produces its own anatomical and clinical picture. The thromboses of certain vessels, as the intracranial sinuses, the portal vein, the femoral vein, are well

characterised, distinct affections, which receive separate consideration in medical books. But I know of no modern work which presents in a systematic and thorough way the anatomical and clinical characters of occlusion of each of the important vessels of the body; although scattered through medical literature is a large and to a considerable extent unutilised casuistic material for such monographic treatment. In this article, treating of the subject as a whole, the more general considerations concerning the effects of thrombosis, with special reference to certain common and clinically important localisations which do not receive separate treatment elsewhere in this work, will be presented. Widely different are the effects according as the thrombosis is cardiac, arterial, capillary, or venous.

Of cardiac thrombosis.—If the presence of globular cardiac thrombi could be determined during life, it would be generally recognised as an index of grave impairment of the heart's action. But, apart from furnishing emboli, ordinary globular thrombi are not known to occasion any symptoms. There may be instances when during life cardiac thrombi may be suspected as more probable sources of emboli, particularly of those causing pulmonary infarction, rather than either endocardial vegetations or venous or arterial thrombi; but beyond conjecture the diagnosis can hardly go. Gerhardt attributed to the pressure of thrombosed auricular appendages upon the pulmonary artery or aorta murmurs heard over the arterial orifices of the heart; but other causes of such murmurs are commoner and better recognised. The encroachment of massive thrombi and of pedunculated polyps upon the orifices of the heart may occasion murmurs, thrills, and symptoms indistinguishable from those of valvular disease. In three such cases, involving the mitral orifice, von Ziemssen observed gangrene of the feet, which he was inclined to refer to arterial thrombosis rather than to embolism; but this symptom has not the diagnostic value which he assigns to it, for in other cases it was present only exceptionally, and it may occur in ordinary mitral stenosis. Unless the orifices are encroached upon, the mere presence even of large thrombi usually occasions little or no disturbance of the heart, or none which can be distinguished from that of associated valvular or mural disease. The clinical features of ball-thrombi have already been considered (p. 188).

Of arterial thrombosis.—The effects of arterial thrombosis are so much like those of embolism that it will be convenient to defer the detailed consideration of their manifestations in common to the article on embolism (p. 235), and here to speak only of the more distinctive features and clinical types of arterial thrombosis.

Whether the occlusion of an artery be by a thrombus or an embolus, the result, apart from possibly infective properties of the plug, depends upon the possibility of establishment of an adequate collateral circulation. If the anastomoses are such as to permit the ready development of a collateral circulation, an arterial branch may be plugged without any mechanical effects. In the case of certain visceral arteries, as the

terminal cerebral, branches of the splenic, and of the renal, a collateral circulation sufficient to nourish the part supplied by the occluded artery cannot be established, even with a slowly-forming thrombus. In some situations, however, arteries whose abrupt obstruction by an embolus may cause the gravest lesions and symptoms, may be closed gradually by thrombus without serious consequences. This has been observed in thrombosis of various arteries of the extremities, neck, and trunk; as the femoral, the iliac, the carotids, the mesenteric, the cœliac axis, a main division of the pulmonary artery, and even the aorta. But in order to secure whatsoever advantage may accrue from its slower formation, the thrombus must find other conditions favourable for the development of a collateral circulation; and often enough these conditions, of which the most important are integrity of the arterial walls and vigour of the general circulation, are absent. Furthermore, thrombosis is often rapid in attack, and hence, whether the plug be a thrombus or an embolus, the result is frequently the same.

In the differential diagnosis between arterial thrombosis and embolism emphasis is properly laid in the former upon the more gradual appearance of the symptoms of vascular occlusion and pre-existing arterial disease, and upon sudden onset and the detection of some source for an embolus, particularly cardiac disease, in the latter (see Diagnosis of Embolism, p. 253). But mistakes in diagnosis are sometimes unavoidable; for all the clinical phenomena which attend the one may occasionally be associated with the other form of arterial obstruction. Nor can the distinction always be made, with the desired precision, at the autopsy, although generally this is decisive. Hence cases are reported as arterial thrombosis which are doubtless embolism, and conversely.

Within recent years primary arterial thrombosis, occurring independently of chronic diseases of the arteries, has been recognised as a more frequent and important affection than had been generally supposed since the acceptance of Virchow's doctrine of embolism. Of especial medical interest are the primary arterial thromboses, arising oftener as a sequel during convalescence than as an accompaniment of various infective diseases, particularly of enteric fever and influenza. The associations and localisation of these thromboses, as well as the prevailing view that they are infective and referable to an acute arteritis, have already been considered.

Arterial thrombosis of the extremities.—When, as is usual, arteries of the lower extremities are affected, the first symptom is pain in the limb. This is often severe and paroxysmal, and is increased by pressure at certain points in the course of the vessel. The obliterated artery may be felt as a hard, sensitive, pulseless cord; and below it pulsation may be feeble or cease altogether. Before obliteration the pulsations may be of wider amplitude than normal, in consequence of lack of arterial tone (Gendrin, Barié). The leg, especially about the foot and ankle, becomes pale, cold, mottled with blush-red spots, numb and paretic. With loss of tactile sensation there is often increased sensitiveness to painful im-

pressions. There may be diminution or loss of muscular reaction to both galvanic and faradic currents. There may be increased moisture of the skin, and some œdematous swelling of the affected leg. Unless adequate collateral circulation be speedily developed the termination is gangrene. While the extent of the gangrene is in relation to the seat of the obstruction, it varies also according to the collateral circulation; so that with occlusion of the femoral or iliacs it may affect only the foot or even a toe; or with closure of the poplitcal or tibial arteries it may extend as high as the point of obstruction. The gangrene is usually dry; but if septic inflammation or closure of the veins occurs it is likely to be moist. Recovery may follow with loss of the gangrenous part; or death may result from exhaustion, from extension of the mortification, from septicæmia and toxæmia.

The rarer arterial thrombosis of the upper extremities may likewise lead to gangrene; but here the chances for restoration of the circulation through the collaterals are much better.

I have already referred to the relations of thrombosis to senile, spontaneous, and other forms of gangrene (p. 178). Heidenhain and Naunyn hold that arterio-sclerotic thrombosis is the usual cause of diabetic gangrene; but further investigations into the causes of this form of gangrene are needed. Thrombosis of the abdominal aorta presents a group of symptoms which will be described under Embolism (p. 273).

The complex of symptoms called by Charcot "intermittent claudication" may be observed with thrombosis of arteries of the lower extremities, or of the iliacs or abdominal aorta; but it is more common with arterio-sclerosis. The term "intermittent claudication" (boiterie) is used by French veterinarians to describe similar symptoms in horses affected with thrombosis of the iliac arteries, which is not a rare disease in these animals. In these cases the lower extremities receive enough blood for their needs during repose, but not during active exercise. The slighter manifestations consist only in some muscular weakness and numbness of the legs after exercise; but in more severe cases, after walking a quarter of an hour or perhaps less, occur great muscular weakness, numbness, and pains and cramps in the legs, which may become cold, exsanguinated, sometimes cyanosed in the periphery, and almost pulseless. All of these symptoms disappear after repose, perhaps of but a few minutes' duration. Charcot's syndrome has in a number of reported cases been a precursor of arterio-sclerotic gangrene, but it may exist for years without this event. The phenomena are unilateral or bilateral, according to the seat of the arterial obstruction. Spasm of the arteries is evidently an important element in the pathogeny of intermittent claudication.

Other evidences of inadequate collateral circulation with arterial thrombosis of the extremities may be muscular atrophy and so-called trophic disturbances, which are generally the result of traumatism or of some infection in the member whose natural resistance is lowered by the imperfect blood-supply.

Thrombosis of the visceral arteries may produce lesions and symptoms identical with those following embolism, such as sudden death from thrombosis of the pulmonary artery, of the coronarics of the heart, or of the basilar; ischæmic cerebral softening, and infarctions of the lungs, heart, spleen, kidneys, retina, and intestine, with their attendant symptoms.

Thrombosis of the pulmonary artery.—It is especially to be noted that thrombosis of the pulmonary artery, both in its principal divisions and in the smaller branches, is often entirely latent, both as regards resulting lesions in the lungs and the symptoms. Thrombosis of the main trunk or primary branches may, however, produce sudden or rapid death; or a sub-acute or chronic affection characterised by dyspnœa, cyanosis, hæmoptoic infarctions and incompetency of the heart, as in a case reported by Blachez.

Dr. Newton Pitt believes that thrombosis of the pulmonary arteries is far more frequent than is generally supposed, even going so far as to say "that thrombosis in the pulmonary artery, so far from being very rare, possibly occurs more frequently than in any other vein or artery in the body." This opinion is based partly upon failure to find a source for an embolus; in the right heart or systemic veins, and partly upon absence of folding, fracture, or other appearances of the plug suggestive of an embolus, as well as upon association with general conditions known to dispose to thrombosis. A similar remonstrance against the current interpretation of so many plugs in the pulmonary arteries as embolic in origin was made by Bristowe in 1869. In my experience sclerosis and fatty degeneration of the intima of the pulmonary vessels is not particularly uncommon; and I also believe that primary thrombosis of the pulmonary arteries, particularly of medium-sized and smaller branches, is more frequent than is usually represented in text-books. Still, for reasons to be considered under Embolism (p. 262), the evidence seems to me in favour of the usually accepted opinion that the majority of plugs found in the pulmonary artery and its main divisions in cases of sudden death are emboli.

Thrombosis of the coronary arteries of the heart.[1] *Cardiac infarction.*—Although the general subject of infarction from arterial occlusion is reserved for the article on embolism, infarction of the heart is caused so much more frequently by thrombosis than by embolism that it is more appropriately considered here.

Thrombosis of the coronary arteries is in the great majority of cases an incident of angio-sclerosis of the heart, an affection of great clinical importance. It may also result from acute or chronic endaortitis near the orifices of these arteries, and possibly from acute inflammation of the coronary arteries. Thrombotic vegetations, springing from the aortic valves, have been known to block the mouth of one of the coronary arteries.

[1] I regret not to have noticed that this subject had been presented by Sir R. Douglas Powell in vol. v. p. 899. The paging cannot now be altered.

There has been much discussion concerning the existence of anastomoses of the coronary arteries. It has been demonstrated that anastomoses exist between the main trunks of these arteries, the most important being those between the auriculo-ventricular branch of the left coronary and branches of the right coronary in the sulcus on the posterior surface of the heart, forming a horizontal or equatorial auriculo-ventricular circle (Haller), and those between the anterior and the posterior inter-ventricular branches near the apex of the heart, forming a vertical or meridional circle. There are also anastomoses on the surface of the left auricle between branches of the left coronary and those of the left bronchial artery. There are, however, no anastomoses between the branches of the coronary arteries after they have penetrated the myocardium, these intramuscular branches being anatomically terminal arteries.

These anastomoses do not usually suffice for the nutrition of the heart after rapid occlusion either of the main trunks or of intramuscular branches. Thrombosis of one of the coronary arteries may be the cause of sudden death. Barth reports the case of a robust young man, aged thirty, who died suddenly when in apparently the best of health. At the autopsy it was found that the mouth of the right coronary artery was blocked by a thrombus, the size of a pea to a bean, attached to a small atheromatous patch of the aorta, close to the opening of the right coronary. By a singular fatality this first and only atheromatous patch to be found anywhere in the otherwise perfectly healthy body had formed at the particular point where the small thrombus springing from it stopped one of the streams feeding the very fountain of life.

Porter has shown experimentally that the frequency of arrest of the heart after closure of the coronary arteries is in proportion to the size of the artery occluded; and that when arrest occurs it is preceded by a fall of aortic pressure and an increase of the diastolic intraventricular pressure. This increased intracardiac pressure checks the flow of blood in the coronary veins, and thus interferes with the coronary circulation in the entire heart.

There are, however, many recorded cases which demonstrate that the main trunk of one of the two coronary arteries may be plugged by a thrombus without causing sudden death. In an instance reported by Dr. Percy Kidd the patient suffered from extremely irregular and weak action of the heart, shortness of breath, and paroxysms of dyspnœa; and gradually sank from cardiac failure. The right coronary artery, about three-quarters of an inch from its origin, was blocked throughout by a firm, partly decolourised, adherent thrombus. The left coronary, particularly its descending branch, was greatly narrowed by selerosis. There were no infarctions or fibroid patches in the heart. Chiari has reported an instance of thrombotic occlusion of the main stem of the right coronary giving rise to an embolus which lodged in the main trunk of the left coronary artery. Sudden death was caused by the latter. In areas supplied by the right coronary were ischæmic infarctions

showing reactive inflammation. These, as well as the symptoms and the appearance of the thrombus, indicated that the main trunk of the right coronary artery had been closed for at least several days before death.

If the patient lives long enough, the usual, but not absolutely imperative, anatomical result of thrombosis either of the main trunks or of intramuscular branches of the coronary arteries, is infarction in the area supplied by the occluded artery. As the descending or anterior interventricular branch of the left coronary is by far the most frequent seat of sclerosis and consequent thrombosis, the infarct is most commonly situated in the lower part of the interventricular septum and of the anterior wall of the left ventricle. The size of the infarct corresponds in general to that of the occluded artery; but, as a rule, the infarct occupies only a part, sometimes but a small part, of the area previously supplied by the obstructed vessel. Unlike infarcts in most other situations, those of the heart are not, as a rule, typically wedge-shaped, but are often irregular in outline, and sometimes appear as if several smaller areas of infarction had coalesced; indeed there may be multiple, detached infarcts resulting from occlusion of a single artery. Both pale, anæmic infarcts and hæmorrhagic infarcts occur in the heart, but the former are the more common. Fresh, anæmic infarcts are swollen, firm, of an opaque yellowish-white colour, and often present in the margin a zone of hyperæmia and hæmorrhage. Microscopically, they are the seat of typical coagulative necrosis; the muscle fibres being devoid of nuclei, indistinctly striated or homogeneous, and of brittle consistence. The term myomalacia cordis, introduced by Ziegler, is not a good designation of most fresh infarcts of the heart. The infarct usually reaches the endocardium, which then presents a mural thrombus; and it may extend to the pericardium and cause a localised fibrinous pericarditis. A reactive inflammation leading to the ingrowth of granulation tissue appears in the margin of the infarct, which, in course of time, is absorbed and replaced by scar tissue, unless it become infected and suppurate.

Cardiac infarction may be the cause of rupture of the heart, or of a parietal aneurysm; or may result simply in a fibroid patch. It is more common than would appear from the meagre attention usually given to the subject in text-books, and is of much anatomical and clinical interest.

The symptoms associated with coronary thrombosis are those of the angiosclerotic heart, so that it is hardly possible to make a positive diagnosis of thrombotic occlusion of the coronary arteries. Irregular, often slow pulse, shortness of breath, precordial distress, angina pectoris, sudden death, all these may occur from sclerosis of the coronary arteries, either with or without thrombosis. Fibroid myocarditis is often present and directly referable to arterial obstruction; but the changes in the myocardium are probably of much less clinical importance than the underlying disease of the coronary arteries. R. Marie has recently published

a valuable monograph on infarction of the myocardium and its consequences, with a full consideration of the previous literature and the addition of many new observations.

Thrombosis of the mesenteric arteries will be considered with embolism of these arteries (p. 268).

Thrombosis of the cerebral vessels will be described in the part of this work treating of diseases of the brain in the next volume.

Here may be mentioned the interesting observations of recent years concerning the dependence of certain diseases of the spinal cord upon affections of the blood-vessels of the cord, arterial thrombosis being an especially important factor in many of these cases.

Capillary thrombosis.—In consequence of the abundant anastomoses, it is only when all or nearly all of the capillaries of a part are thrombosed that any mechanical effects result. Such extensive capillary thrombosis is more frequently the result than the cause of necrosis of a part. According to von Recklinghausen, superficial, often extensive, necrosis of surfaces, as of the skin and mucous membranes, may be caused by widespread hyaline thrombosis of capillaries resulting from the energetic action of thermic, chemical, and even mechanical agents. In frost-bites and burns there may be extensive local hyaline thrombosis of capillaries and small vessels. I have already referred to my observations of anuria in swine, caused by extensive hyaline thrombosis of the renal capillaries (p. 161). Although in many cases I have seen similar hyaline thromboses in human kidneys, they were never so extensive as to seem likely to cause recognisable symptoms. Several years ago I drew attention to the presence of hyaline in capillaries and arterioles in the walls of some fresh gastric ulcers, and since then I have been able to repeat the observation in three or four instances.

Effects of venous thrombosis.—Thrombosis is so pre-eminently an affection of veins that chapters in text-books treating of the general subject usually pay scant attention to its occurrence in other parts of the circulatory system. In the veins thrombosis occupies the field of intravascular plugging almost alone, for it is only in the portal system, and in the rare instances of retrograde transport, that embolism enters into consideration; such extraordinary occurrences as embolism of the azygos vein, resulting from thrombosis of the inferior vena cava, reported by Löschner, being mere pathological curiosities.

The direct effects of venous thrombosis, as of arterial, are referable to the mechanical obstacle to the circulation and to the properties of the thrombus. The mechanical effects result from inadequacy of the collateral circulation. The free venous anastomoses in many parts of the body prevent any disturbance of the circulation as a result of venous occlusion by simple or benign thrombi. Such innocuous thromboses are particularly common in the pelvic veins. In some situations veins, whose rapid occlusion may cause serious lesions and symptoms, may be slowly plugged by a thrombus without manifest harm. For example, it is not uncommon to find at autopsy the main trunks of

the renal veins completely thrombosed, without consequent alteration of the kidney or corresponding symptoms during life; although we know that ligation of these veins causes hæmorrhagic infarction of the kidney with albuminous, bloody urine.

Frequently, however, the contrast between the effects of ligation and those of thrombosis of veins is in the other direction; the thrombosis being followed by venous congestion, and the ligation of the same veins being without evident disturbance of the circulation. The latter difference is not always easy to explain; but the factors to which we can often appeal with more or less success, in attempting to account for the absence of sufficient collateral circulation with venous thrombosis, are the extent of the occlusion, general debility, feebleness of the circulation in consequence of coexistent anæmia, infection, cachexia or constitutional disorder, generally high venous pressure and low arterial pressure, lack of muscular movement and perhaps of other subsidiary forces aiding venous circulation, phlebosclerosis, inflammation or some less evident affection of blood-vessels called upon for extra work, and irritative or toxic properties of the thrombus. The importance of these, and perhaps other accessory conditions, in explaining the passive congestion of many venous thromboses in human beings is made evident, not only by the inability to produce similar effects experimentally by correspondingly slight or moderate degrees of venous obstruction, but also by the varying effects of thrombotic processes with the same localisation and extent in different persons and under different conditions. Thus femoral thrombosis may be attended by absolutely no œdema or passive congestion, or may occasion extreme degrees of œdema and venous congestion.

The consequence of the passive hyperæmia caused by venous thrombosis is local dropsy. This constitutes the characteristic symptom of uncompensated venous obstruction by a thrombus, as local necrosis does that of uncompensated arterial thrombosis. In addition to the œdema, there may be diapedesis of red corpuscles, but this occurs to a perceptible degree only when the obstruction to the venous flow is extreme, or the capillaries unusually permeable. Such hæmorrhages are very rare in peripheral venous thrombosis, but are common with thrombosis of the portal and mesenteric veins, the cerebral veins and sinuses, the splenic, the retinal, and some other visceral veins. Actual necrosis may likewise result from thrombosis of the mesenteric, cerebral, and splenic veins; but, if it occurs at all with thrombosis of veins of the extremities, it is extraordinarily rare, and probably due to complications.

In addition to these effects, due directly to the blocking of the venous circulation, even so-called benign or simple thromboses often set up an acute inflammation in the venous wall and surrounding part; or, as already explained, this inflammation may antedate the thrombosis. These chemical, as distinguished from mechanical, effects consist chiefly in arterial hyperæmia, inflammatory œdema, pain, implication of nerves, and constitutional symptoms, such as chills, fever, and quickened pulse. The occurrence of these irritative or toxic effects, even with the so-called

marantic thromboses, is an argument (in addition to those already considered) in favour of the infective nature of many of these plugs, and of their primarily phlebitic origin. But while undoubtedly significant of such an interpretation, it can hardly be considered conclusive; for it is possible that certain thrombi may possess irritative properties not attributable to the presence of micro-organisms or their products, and that the phlebitis, as well as the periphlebitis, may be secondary. However this may be, the old distinction between benign and infective thrombi no longer appears so sharply marked as was once supposed.

In rare instances the venous medical thromboses associated with anæmic, infective, cachectic, and constitutional diseases are plainly septic, and give rise to phlegmons, and perhaps pyæmia or septicæmia. The suppurative or septic thrombophlebitis, which with its attendant pyæmia was in præ-antiseptic days such a common and formidable wound complication, belongs to the surgeon's domain, or, in puerperal sepsis, to the obstetrician's. (See arts. "Pyæmia" and "Puerperal Septic Disease" in vol. i.) To the borderland of medicine and surgery belong certain septic thrombophlebitides of visceral veins, of which the most important medical group, those of the portal system, has been considered by Professor Cheyne (vol. i.), and by Dr. Davidson in his article on "Suppurative Hepatitis" (vol. v. p. 123). Thrombosis of the umbilical vessels, which may occur either before or after birth, may be either simple or septic. The latter is an important affection, the consideration of which belongs to treatises on diseases of infants.

There is perhaps no pathological phenomenon which, on the face of it, appears simpler of explanation than the local œdema consequent upon venous obstruction, but which, the more it is investigated, turns out to be, or at least is made to appear to be, more complicated. The explanation which naturally occurs to one, and which is often given, is that the œdema is due simply to increased filtration of serum from the blood, in consequence of the rise of intravenous and intracapillary pressure resulting from the obstruction to the venous circulation. It is certain that this simple explanation does not suffice, at any rate for most venous thromboses, and that factors other than the mere rise of blood-pressure in the veins and capillaries are concerned; but as to the nature of these other factors there is great difference of opinion. The whole problem is wrapped up with that of the hypotheses of lymph-formation and lymph-absorption, so lively at the present day, into the discussion of which it is impossible here to enter. Corresponding to the two classes of these hypotheses, we have mechanical hypotheses and vital or secretory hypotheses of the œdema of passive congestion. The mechanical explanations are at least easier of comprehension. Cohnheim attributed this form of œdema to increased venous and capillary pressure, combined with increased permeability of the capillary wall due to malnutrition.[1] Starling and

[1] Cohnheim is sometimes quoted as considering increased pressure a sufficient explanation of mechanical œdema, although in his *Allgemeine Pathologie*, Bd. i. p. 494, he expressly recognises as an additional factor "unknown influences on the part of the living vessel-wall." As I had opportunity, when working in his laboratory on a problem concerning œdema, to

Cohnstein, with full knowledge of the later work, to which they have made important contributions, are advocates of a similar explanation.

Doubtless several factors, although not all necessarily operative in the same case, are concerned in the causation of the œdema of venous thrombosis. Those which seem to me most apparent are the following: (i.) increased intra-venous and intra-capillary pressure, with consequent increased transudation of serum (not alone sufficient, for tying the femoral vein or inferior vena cava generally causes no œdema); (ii.) increased permeability of the capillary walls, which may be due to various causes, such as stretching from larger content of blood, starvation and asphyxia of capillary endothelium from lack of fresh supply of nutriment and oxygen, and injury from abnormal composition of blood in anæmic, infective, cachectic, and constitutional disease, or from inflammatory irritants; (iii.) diminished absorption of lymph in consequence of lack of muscular movement, of imbibition of the capillary walls with fluid, and especially of retarded capillary and venous flow; (iv.) arterial dilatation from irritative or inflammatory influences emanating from adjacent thrombosed veins, probably also from the asphyxiated tissues, and acting either directly upon the arterial wall, or directly upon vaso-motor nerves, or reflexly (here the conditions resemble those in Ranvier's well-known experiment of tying the inferior vena cava or femoral vein, and producing vaso-motor paralysis by section of the sciatic nerve); (v.) sometimes a watery condition of the blood rendering it easier of filtration. Experiments of Dr. Lazarus-Barlow indicate that changes in the chemical composition of the tissues and tissue-fluids are also a factor in the production of the œdema.[1] The influence of hydrostatic pressure is evident from the greater frequency of œdema with thrombosis of the lower than of the upper extremities, and from the effect of position upon the amount of the œdema. While these various factors can be conceived as essentially physical and chemical in their action, the living capillary wall upon which they act, either directly or indirectly, is to be thought of as something different from a dead animal or artificial membrane.

Opposed to these mechanical explanations are the secretory hypotheses of œdema, of which Hamburger and Lazarus-Barlow are leading exponents. Of especial importance is the work of Lazarus-Barlow upon the œdema of passive congestion. He finds all the physical explanations inadequate; and, upon the basis of interesting experiments, he concludes that a principal factor is increased secretion of lymph by the capillaries incited by starvation of the tissues and accumulation of waste metabolic products. His *Manual of General Pathology* may be consulted for a full presentation of his views and a criticism of the mechanical hypotheses of œdema.

become familiar with his views on this subject, I may be permitted to say that he often spoke of increased permeability of the capillary wall as an essential factor in the explanation of the œdema of passive congestion.

[1] To these changes, as the cause of alterations in osmotic pressure, Loeb (*Pflüger's Archiv*, 1898, lxxi. p. 457) assigns the chief importance in the production of œdema.

The œdema of phlegmasia alba dolens is by no means all due to venous congestion. Much, sometimes most of it, is an inflammatory œdema spreading from the thrombosed veins. This is evident partly from the hard, brawny, painful, at times warm character of the swelling (œdema calidum); and partly from its location in the part of the extremity nearest the affected veins. The œdematous swelling may begin above and extend downwards, instead of in the usual direction from below upwards. The hydrarthrosis often associated in moderate degree with phlegmasia is probably also referable to an inflammatory serous exudate rather than to passive transudation from venous obstruction. It occurs especially in the knee-joint.

Thrombosis of veins of the extremities.—Clinically the most familiar form of venous thrombosis is that of the extremities; the lower much oftener than the upper. Its various sites and clinical associations have already been considered (pp. 179 and 191). The affection may be entirely latent; or may be recognised by a slight or moderate unilateral œdema without general or other local symptoms; or may be in the form of well-marked phlegmasia alba dolens; or rarely may assume a severely infective character, with chills and high fever; or, exceptionally, may lead to phlegmon and pyæmia or septicæmia. There is every transition between the extremes. The latent and milder types occur especially with tuberculosis, cancer, and other cachexiæ; the more severe manifestations with phlebitis of the puerperium, infective diseases, and chlorosis; but there are many exceptions to this rule.

In the more acute and well-characterised cases the general symptoms are chiefly manifest at the onset; and consist in moderate elevation of temperature, rarely preceded by a distinct chill, oftener by chilly sensations and quickened pulse. Increased frequency of the pulse may antedate the rise in temperature, and the pulse may remain rapid after the temperature falls. This disproportion between pulse and temperature is of diagnostic value (Mahler, Wyder, Singer),[1] but it is not always present. These general symptoms of the initial stage, which may persist for days, are often overlooked; or they are masked by an existing febrile disorder. They are probably present in some degree, even in mild cases, oftener than the clinical records show.

The characteristic symptoms are the local ones in the affected leg. Pain, often paroxysmal, is usually the first to attract attention; but sometimes it is the œdema. The pain may be severe. It is more or less generalised, with especial tenderness in the groin, the inside of the thigh, the popliteal space, and the calf. Often it is first noted and may remain localised in the calf; as is true of the œdema also. There may be sensations of numbness or of "pins and needles." The cardinal symptom, œdema, sometimes descending sometimes ascending, gives rise to the firm, painful swelling of the limb, covered with tense, shiny, smooth, white or mottled skin, marked often by dilated veins, whence

[1] Singer (*Arch. f. Gynäk.* 1898, lvi. p. 218) has made a careful study of the pulse-curve in puerperal thrombosis. A step-like acceleration of the pulse-curve often precedes other manifestations of thrombosis by several days.

comes the name milk-leg or white leg. The œdema in typical phlegmasia alba dolens is hard and elastic, pitting but little on pressure. Occasionally the skin has a more livid, cyanotic hue, or it may be of a brighter red. In the more acute cases the surface temperature is elevated; in others it is often lowered. Muscular movements are naturally restrained, and it is said there may be actual paresis. The thrombosed vein, if accessible to palpation, can often be felt as a hard, tender cord; but it is best not to attempt to gain this information, which in most cases is of little practical importance. The sensation obtained from palpating the vein may be misleading in consequence of the periphlebitis, or of the soft character of the thrombus. Certainly, in view of the manifest danger of detaching an embolus, only the gentlest manipulations are permissible. If the thrombosed vein be superficial, it may sometimes be seen as a line of livid redness beneath the skin. It is not always tender on palpation.

The great and usually the only danger from peripheral thrombosis is fatal pulmonary embolism. It occurs oftenest between the second and fourth weeks, but may occur earlier or later. The danger may be considered to be past at the end of six weeks, if the local symptoms have subsided; although there are exceptional instances of pulmonary embolism at a later period. It is to be noted that pulmonary embolism may result from latent and mild forms of venous thrombosis as well as from those of the well-marked examples; it is, however, rare with the cachectic thromboses of tuberculosis and cancer. Small pulmonary emboli usually cause no lesions or symptoms, yet they may give rise to hæmorrhagic infarction, or embolic pneumonia.

Nervous phenomena are sometimes so prominent as to have led to the recognition of a neuralgic type of phlebitis (Graves, Trousseau, Quenu). There may be even a mild peripheral neuritis associated with the venous thrombosis. This is probably caused by the direct action of inflammatory irritants spreading from the inflamed veins; but it has also been attributed to thrombosis of small veins in the nerve-trunks, to the bathing of the nerves in the œdematous fluid, and to reflex irritation. Occasional sequels of femoral thrombosis, for the most part very rare, are varicose veins, leg ulcers, persistent chronic œdema, elephantiasis, muscular hypertrophy, muscular atrophy, and club-foot.

There has been much discussion on the possibility of gangrene being caused by thrombosis of the femoral or iliac veins. Cases have been reported in which no other cause of the gangrene was found than venous thrombosis; but with peripheral venous thrombosis this is such an exceptional occurrence that it seems clear that, when gangrene results, complicating factors—such as arterial disease, pressure upon arteries, arterial spasm, great feebleness of the circulation or septic inflammation—must be associated with venous thrombosis. It is true that surgeons are familiar with gangrene after ligation of the femoral vein, but here also the result is exceptional and attributable to some complication. Braune, upon anatomical grounds, attempted to demon-

strate that gangrene is to be expected after closure of the femoral vein near Poupart's ligament, but the clinical evidence does not support this view. Galliard has reported a case and has collected from the records others in which gangrene had followed venous without arterial thrombosis.

The thromboses of the upper extremities are usually of shorter duration and milder type than those of the lower; unless referable to some persistent cause, such as the pressure of a tumour. They are often accompanied by some cervical œdema.

Thrombosis of the inferior vena cava.—Since the days of Richard Lower occlusion of the inferior vena cava has been the subject of much experimental and clinical study. There are reports of at least 140 cases of this affection in human beings. The principal records are cited in the monographs of Vimont and Thomas, although the bibliography is by no means complete. Thrombosis of this vein is rarely autochthonous. Usually it is continued from the femoral or pelvic veins through the iliacs, or is due to some abdominal disease, as the pressure of a tumour. It may occur without any symptoms or without symptoms suggestive of the diagnosis. The characteristic symptoms are œdema of both lower extremities and of the abdominal walls, and the development of a typical collateral circulation. When the renal veins are likewise occluded there may be albuminous, bloody urine; but with thrombosis of these veins this symptom is oftener lacking than present. The diagnosis rests especially upon the appearance of dilated anastomosing veins coursing upwards from the groins and flanks over the abdominal walls and lower part of the thorax. These tortuous, varicose veins, sometimes as big as the little finger, make a very striking and characteristic picture. The superficial veins concerned in carrying on the collateral circulation are the inferior and superior superficial epigastric, the long thoracic, the superficial circumflex iliac, the external pudic, the lumbo-vertebral anastomotic trunk of Braune and numerous unnamed anastomotic veins. The direction of the circulation is of course from below upward. In addition there is a deep collateral circulation through various visceral veins with dilatation of the azygos veins. Sometimes the circulation is almost wholly through the deep collaterals, and there may be little or no dilatation of the visible superficial veins. In fact, in not a few cases, by the absence of visible dilated collaterals, the diagnosis is rendered difficult or impossible. Schlesinger has observed and collected a number of cases where the œdema was in one leg only. This may be due to the previous establishment of a collateral circulation on one side from a former iliac thrombosis, or to unilateral iliac thrombosis with parietal thrombosis of the vena cava, or to congenital duplication of the vena cava.

Thrombosis of the renal veins.—This affection is fairly common. It may be an extension of a thrombotic process in the vena cava, or on the other hand the latter may be secondary to renal thrombosis. Marantic thrombosis of the renal veins is not unusual in infants with cerebral symptoms, or exhausted by diarrhœa. In adults thrombosis of the renal veins is observed not very infrequently in chronic

Bright's disease, particularly the waxy kidney; and in malignant tumour of the kidney. The renal veins rank among those predisposed to marantic thrombosis. I once made an autopsy on a case of primary genito-urinary tuberculosis in which a caseous mass had broken into a renal vein which contained an adherent grayish-red thrombus extending into the vena cava. Tubercle bacilli were present in the caseous mass and the thrombus. There was acute miliary tuberculosis. The lesions and symptoms which one would expect to find with thrombosis of the main trunk of the renal vein are oftener absent than present. The various collateral veins, communicating through the capsule and along the ureters with the lumbar, diaphragmatic, adrenal, spermatic, and other veins, suffice for adequate return flow. Still a number of cases have been observed with more or less hæmaturia and albuminuria which have been referred to thrombosis of one or both renal veins, and genuine hæmorrhagic infarction may occur.

Thrombosis of the mesenteric veins.—Thrombosis of veins in the intestinal wall is often associated with ulcers and other morbid conditions in the intestine. The thrombus may extend into the small mesenteric veins, or the latter may be attacked independently. These small thrombi are important chiefly as a source of infective emboli transported to the liver.

Thrombosis of the large mesenteric veins is less frequent than embolism or thrombosis of the mesenteric arteries. I have reported an instance of this affection, and have found reports of 31 additional cases with pronounced symptoms, and of a few cases without symptoms referable to the thrombus and without intestinal lesion. The references will be found at the end of this article. The superior mesenteric vein was thrombosed much oftener than the inferior. In many cases with symptoms, the thrombosis was ascending and secondary to inflammation, ulceration or some other disease of the intestine; in some instances it was descending from thrombosis of the portal or splenic vein; in a few it was secondary to enteric fever or some marasmic or cachectic state; in one it was attributed to a calcific plate adjacent to the vein, and in one it followed splenectomy. The symptoms are the same as with occlusion of the mesenteric arteries (see art. "Embolism," p. 268), but as a rule are even more violent in character and rapid in course. They are as follows: sudden onset of very intense, colicky, not definitely localised abdominal pain; distended, tender, tympanitic abdomen; vomiting, which may be bloody; obstipation or bloody diarrhœa; and rapid collapse with cold sweat and subnormal temperature. The diagnosis is likely to be acute ileus, and laparatomy to be performed. Death generally occurs within two or three days. The symptoms may, however, be less violent, and the course less rapid than those mentioned. At the autopsy are found hæmorrhagic infarction and gangrene of the intestine, hæmorrhages in the mesentery, bloody fluid in the peritoneal cavity, and sometimes, although not regularly, peritonitis. The cases without symptoms have been usually thromboses of slower formation, but this does not appear to have been always the case.

In a case reported by Dr. Rolleston, the superior mesenteric vein was filled with softened, canalised clot; and in addition the inferior mesenteric vein, the internal and external iliac veins on both sides, and the splenic vein were completely thrombosed, and a partly occluding thrombus extended into the portal vein. The thrombus in the superior mesenteric vein was regarded as the oldest. There was old and recent inflammation of the intestine, but no intestinal infarction.

Of interest is the relation of thrombosis of the mesenteric veins to portal thrombosis. In several instances of the latter thrombosis of the mesenteric veins occurred without hæmorrhagic infarction of the intestine. Doubtless the explanation is that a sufficient collateral circulation had been established after the portal thrombosis to prevent the usual effects of a subsequent mesenteric thrombosis. That this, however, is not always the case is shown by the sudden or more gradual termination of some instances of portal thrombosis with hæmorrhagic infarction of the intestine, in consequence of the extension of the thrombus into mesenteric veins. This has occurred especially in the more acute cases of portal thrombosis, but it may occur also in those of several months' duration. Acute portal thrombosis may cause hæmorrhagic infarction of the intestine without mesenteric thrombosis; or the infarction may be over a larger extent of intestine than corresponds to the thrombosed mesenteric veins. On the other hand, the infarcted area may be much smaller than that supplied by the thrombosed vein. The symptoms may be of slower development and of milder type when thrombosis of the mesenteric veins is secondary to portal thrombosis than when it is primary. The sequence of events in Fitz's case is interesting—globular thrombi in the left ventricle, embolism and infarction of the spleen, secondary thrombosis of the splenic vein, extension of the thrombus into the superior mesenteric vein, hæmorrhagic infarction of the intestine terminating fatally. There was no obstruction in the mesenteric arteries.

Pylethrombosis.—The septic variety of thrombosis of the portal vein (suppurative pylephlebitis) having been described (vol. i. p. 610, and vol. v. p. 127), it remains to speak here of simple portal thrombosis, often called without much propriety adhesive pylephlebitis. This is a well-characterised, although usually not readily-diagnosed affection. It is caused most frequently by compression either of the intrahepatic branches of the portal vein in cirrhosis, syphilis, or tumours of the liver; or of the main branches or trunk by fibrous perihepatitis, chronic peritonitis, swollen lymph-glands, impacted gall-stones or tumours. Other causes are diseases of the walls of the portal vein, either primary or propagated from some neighbouring focus; extension of a thrombus from the splenic or mesenteric veins; pancreatic disease; gastric cancer; ulcer, or other gastric or intestinal disease; infective and toxic diseases; puerperal eclampsia (Schmorl); marasmus, and traumatism. Sclerosis and calcification of the wall of the portal vein deserve more attention as causes of portal thrombosis than

they have usually received. To the 12 cases collected by Spiegelberg and Borrman in which this was the cause, is to be added A. A. Smith's case, in which I made the autopsy. There was extensive calcification and thrombosis of both splenic and portal veins in a man about 60 years old, who died of gastric hæmorrhage. He had previously vomited blood on several occasions. There was rapidly increasing ascites. Calcification of the media of the portal vein may occur without marked affection of the intima. Marantic portal thrombosis is very rare, and, according to Schüppel, occurs chiefly as a terminal event without characteristic symptoms. Nonne, however, in reporting a case of marantic thrombosis from Erb's clinic, interprets several previously reported instances with marked symptoms as belonging to this variety. The thrombus may become organised and the vein converted into a fibrous cord, as in a case reported by Osler.

The symptoms are those of portal obstruction—ascites, hæmatemesis and enterorrhagia, splenic enlargement, dilatation of superficial abdominal veins, and progressive marasmus. The caprices of venous thrombosis are evident here as elsewhere. Characteristic symptoms may be entirely lacking, or one or more of the important symptoms may be absent. Ascites has been absent or slight, especially in cases with abundant hæmorrhages from the stomach and bowels. In general, however, the rapid onset, the intensity of the evidences of portal obstruction, and especially the quick return of ascites after tapping are characteristic of obliterating portal thrombosis; and by observation of these points a correct diagnosis has repeatedly been made. These acute symptoms are of most diagnostic value when they appear in persons previously in apparent health, as has been observed with phlebosclerotic thrombosis; or in the course of some disease not itself a cause of obstruction to the portal circulation. When, as in cirrhosis of the liver, the symptoms unfold themselves gradually, the diagnosis is manifestly impossible, or at best no more than mere conjecture.

I have added traumatism as a possible cause of portal thrombosis on the basis of a diagnosis made by Dr. Delafield, while I was resident physician in his service at Bellevue Hospital. A lad, who had received a severe blow on the abdomen, was admitted with extreme ascites which had come on within two weeks after the injury. He was repeatedly tapped, the clear fluid reaccumulating at first with great rapidity after each tapping, afterward more slowly, until in the course of months there was complete recovery. In the meantime enlarged veins made their appearance over the upper part of the abdomen.

Jaundice is not a symptom of portal thrombosis, although repeatedly observed as a complication. The channels for establishment of a collateral circulation are the same as in cirrhosis of the liver, with the exclusion of those which communicate with the portal vein itself, at or beyond the site of occlusion.

Under certain exceptionally favourable conditions recovery may take place; a satisfactory collateral circulation being established, with perhaps

opening of channels through the organised thrombus. The usually fatal termination may be from hæmorrhage or exhaustion, sometimes within a few weeks or even days from the onset. I know of no instance, in man, of death within a few hours after occlusion of the portal vein, such as occurs regularly, with great fall of arterial blood-pressure, after ligating this vessel in rabbits and dogs. As already mentioned, hæmorrhagic intestinal infarction may be caused by portal thrombosis (p. 219).

There has been much discussion on the occurrence of changes in the liver which can be attributed directly to stoppage of the portal circulation. In the majority of cases of portal thrombosis the liver has been the seat of atrophic cirrhosis, but most modern authors have regarded the thrombosis as secondary to the cirrhosis. Dr. Samuel West, however, in 1878, took strong ground in favour of the reverse being sometimes the case; and he found support in the experimental results of Solowieff. The later experiments of Cohnheim and Litten have been widely accepted as indicating that obstruction of the portal vein is without effect upon the hepatic structure and functions. Bermant has recently gone over the entire experimental and anatomico-clinical evidence, and has reached the conclusion that stoppage of the portal vein may lead to atrophic cirrhosis. The case which he reports speaks strongly in favour of this view; for only the right branch of the portal vein was thrombosed, and the cirrhosis was limited to the corresponding lobe of the liver. Nevertheless, cases of portal thrombosis, some not of short duration, have been reported by Frerichs, Leyden, Alexander, and others without any alteration in the liver; and I have observed two such cases in which the symptoms of portal obstruction extended over several months.[1]

Thrombosis of the splenic vein.—Primary thrombosis of the splenic vein and its radicles is rare. I have seen an instance of autochthonous thrombosis secondary to calcification of the wall of the splenic vein. Thrombosis of veins within the spleen, extending sometimes into the main trunk, is common with infarction, abscess, and certain other morbid processes in this organ. Thrombosis of the main trunk may be caused by suppurative or hæmorrhagic pancreatitis, or by cancer of the pancreas. As has already been mentioned, thrombi may extend from the portal or mesenteric veins into the splenic, as well as from the latter into the former. There is the possibility of thrombosis secondary to retrograde embolism of the splenic vein.

Köster has reported the rare complication of enteric fever with thrombosis of the radicles and main trunk of the splenic vein; the evidence being conclusive that the oldest part of the thrombus was in the spleen. The evidences of occlusion of the main vein appeared at the beginning of convalescence. The spleen was enormously swollen and the pulp of a diffuse reddish-black colour. The capsule and surround-

[1] Chiari (*Centralb. f. allg. Path. u. path. Anat.* 1898, ix. p. 854) has recently described endophlebitis, with thrombosis, of the radicles of the hepatic vein. There were symptoms of portal obstruction.

ing tissues were suffused with blood. As there were thrombi in the small mesenteric veins near the ulcerated ileum, there was a possibility of retrograde embolism; but Köster thinks it more probable that the process originated within the spleen.

Thrombosis limited to the extra-splenic part of the vein may be completely or nearly compensated by the collateral venous circulation, so that no changes or only a moderate passive congestion occur in the spleen.

Thrombi occupying intrasplenic veins may cause hæmorrhagic infarction. Dr. Rolleston has observed two instances of anæmic infarcts of the spleen in association with thrombosis of the splenic vein. Litten probably goes too far in attributing most genuine hæmorrhagic as distinguished from pale infarcts of the spleen, to venous thrombosis rather than to arterial embolism.

Extensive necrosis and hæmorrhagic infarction may be caused by torsion of the pedicle of a movable spleen. A perhaps unique instance of this occurrence was observed in the Johns Hopkins Hospital, and has been described by Osler.

Obliteration of the superior vena cava.—Since the admirable studies by Duchek (1854) and by Oulmont (1856) of the causes and symptoms of obliteration of the superior vena cava a considerable number of instances of this condition have been reported. By far the most frequent cause is the pressure of a mediastinal tumour, of swollen lymph-glands, or of an aneurysm. Less common is the growth of a cancer or other malignant tumour into the lumen of the vein. Banti reports a curious case of generalised tuberculosis in which nearly the whole length of the superior vena cava was completely filled by a neoplastic tuberculous mass projecting into the right auricle. The outer walls of the vein were intact. The condition seems to have been analogous to the tuberculous cardiac thrombi already described (p. 184). Primary thrombosis of the superior vena cava is so rare as to be a pathological curiosity. Poynton has reported an instance of thrombotic occlusion of the upper two-thirds of the superior vena cava in association with chronic and acute valvular endocarditis, and in a second case of valvular disease he found a mural thrombus in this vein. In both cases there was tricuspid insufficiency (p. 199). The characteristic symptoms are œdema and cyanosis of the upper half of the body—face, neck, arms, and thorax—and dilatation of deep and superficial veins, especially marked over the anterior wall of the thorax and upper part of the abdomen. In a case exhibited by Dr. Osler to the Johns Hopkins Hospital Medical Society, the anterior surface of the chest was covered with large, spongy bunches of enormous varicose veins, in one of which a phlebolith could be felt. Other symptoms, which may be present, are œdema of conjunctival and buccal mucous membranes, exophthalmos, watery secretion from the conjunctivæ, nose-bleeding, and such signs of venous congestion of the brain as headache, vertigo, and ringing in the ears, especially on bending over. In the light of the whimsicalities of venous thrombosis it is hardly necessary to add

that the symptoms may be less marked, and may deviate from what might naturally be expected.

Thrombosis of the innominate, subclavian, and jugular veins.—The more important literature of this subject is cited in the papers of Pohl, Hirschlaff, and Helen Baldwin. The occurrence of these thromboses in cardiac disease, and from compression, has already been mentioned (p. 199); other rare causes are infection, empyema, acute rheumatism, tuberculosis, marasmus, and traumatism. The symptoms are the usual ones of venous congestion, œdematous swelling, pain in the regions from which the veins convey blood, dilatation of collaterals, and, in the case of the cervical veins, recognition of the thrombosed vein by palpation, which, however, should be done with great care.

Thrombosis of the pulmonary veins may be mentioned as a rare source of embolism in the aortic system. It is usually secondary to some pulmonary disease, as gangrene, malignant tumours, abscess, infarction, tuberculosis, pneumonia. It has been observed with extensive emphysema of the lungs (Schmale).

Thrombosis of the cerebral sinuses will be considered in connection with diseases of the brain in the following volume.

O. Wyss has described a remarkable instance of extensive hæmorrhagic myelitis caused by widespread hyaline and platelet thrombi in veins within the spinal cord. The thrombosis was secondary to a glioma of the dorsal cord. Rosin has likewise observed thrombosis of veins extending the whole length of the spinal cord, consecutive to a tumour of the cervical cord.

Multiple thromboses.—Finally may be mentioned the cases in which many veins in different parts of the body become thrombosed, as in Huels's case of chlorotic thrombosis; and Osler's, of thrombosis secondary to cancer of the stomach, already cited (pp. 201 and 198). Erlenmeyer has described as "jumping thrombosis" (springende Thrombose), in distinction from the ordinary creeping form, cases in which the process attacks first one vein and then another, in a different region, until finally various veins in the extremities, trunk, and brain may become plugged.

Treatment.—The treatment of thrombosis of the extremities is about all that needs special consideration in this article. In view of the part played by enfeebled circulation and secondary infections in the causation of thrombosis, prophylactic measures should be directed toward maintaining good nutrition, strengthening the heart's action, and warding off secondary infection, so far as may be, or treating accessible foci of infection antiseptically.

In the absence of any available medicinal treatment known to have any direct control over the process of thrombosis, the general indications for treatment are to secure as speedily as possible an adequate collateral circulation, in order to ward off the danger of tissue-necrosis or gangrene from arterial thrombosis and the effects of passive congestion from venous thrombosis; and, above all, in the case of venous thrombosis, to guard against the detachment of emboli. These indications are best met by

absolute rest, suitable position and immobilisation of the thrombosed extremity, and nourishing diet.

With venous thrombosis of a lower extremity the patient should lie on the back with the limb elevated on an inclined plane, or in a trough well lined with cotton wool. The limb should be kept warm by wrapping in cotton wadding, and hot fomentations of lead-water and laudanum, or some similar preparation, may be applied. If the condition of the heart indicate it, digitalis or other cardiac tonic may be given. At the height of the process the pain may be so intense as to require the use of opium or some of its derivatives.

It is all-important to know what not to do. The patient should be cautioned against moving the leg, especially against any sudden jerk. Palpation of the affected veins should be of the gentlest sort, and is better omitted altogether. All unnecessary movements and manipulations should be avoided. Nothing is gained, and harm may be done by resorting, before all danger of embolism is passed, to the old-fashioned treatment of rubbing in mercurial or belladonna ointment. The length of time that the patient should remain quiet in bed will vary according to the severity of the case. Although the thrombotic process does not usually progress after the tenth or twelfth day, it is a general rule that the patient should not be allowed to walk in less than forty days. A large number of the deaths from pulmonary embolism have occurred when the patient first walks, or goes to stool, or takes a bath.

Light bandaging of the lower part of the leg assists the circulation; but, if applied at all, it should be with only minimal compression. After the danger of embolism is passed, massage and bandaging may be employed to advantage, or a long elastic stocking worn.

If gangrene result from arterial thrombosis, the time and site of operation should be determined upon surgical principles.

WM. H. WELCH.

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EMBOLISM

Definition.—Embolism is the impaction in some part of the vascular system of any undissolved material brought there by the blood-current The transported material is an embolus. Embolism may occur likewise in lymphatic vessels.

Historical note.—Rudolf Virchow is the creator of the doctrine of embolism. There is scarcely another pathological doctrine, of equal magnitude, the establishment of which is so largely the work of a single man. Not but that there were foreshadowings of this conception before Virchow, notably by Bonetus and van Swieten in the seventeenth and eighteenth centuries, and by Allibert and François in the early part of the present century. A few observers and experimenters, indeed, anticipated some of Virchow's results. The wonder is that until Virchow's time the idea of embolism remained so foreign to medical thought; so obvious and necessary a corollary does it seem to be of the discovery of the circulation of the blood. Between the years 1846 and 1856 Virchow constructed the whole doctrine of embolism upon the basis of anatomical, experimental and clinical investigations, which for completeness, accuracy, and just discernment of the truth must always remain a model of scientific research in medicine. These discoveries introduced new chapters and necessitated a recasting of many old ones in pathology. A number of important morbid conditions, among which pulmonary embolism and cerebral embolism may be especially mentioned, were now for the first time clearly recognised. Virchow's studies of thrombosis and his demonstration that not all intravascular, ante-mortem clots are formed at the place where they are found, and that infarcts are not the result of inflammation and capillary phlebitis, put an end to the false and to us at present almost incomprehensible ideas then prevailing as to the overshadowing importance of phlebitis in pathological processes. Especially was the doctrine of metastasis, which in old days was one of the most mystical

in medicine, greatly expanded and at the same time placed upon an intelligible and firm foundation.

The new fields opened by Virchow have been industriously cultivated by a multitude of workers. The additions to our knowledge have been many and valuable, but they have related mainly to details, and can scarcely be said to have led to new points of view. The works of Bernhard Cohn and of Cohnheim may be signalised as among the most important of the contributions since Virchow's early publications. Cohn's remarkable book, published in 1860, is extraordinarily rich in anatomical, experimental, and clinical facts, and it is well for any one who believes that he has a new observation or opinion concerning embolism to consult it before venturing on publication; a precaution which has evidently been often neglected by writers on the subject.

Varieties of emboli.—Substances of the most varied character, solid, liquid or gaseous, may enter the circulation and be conveyed as emboli. Unless some special epithet be used, an embolus is generally understood to be a detached thrombus, or part of it, including under this designation endocarditic vegetations. Other possible sorts of emboli are fragments of diseased heart-valves, calcific masses, bits of tissue, tumour-cells, parenchymatous cells, animal or vegetable parasites, fat, air, pigment-granules and foreign bodies. Emboli of air, of fat, and of parenchymatous cells will be considered separately. An important classification, as regards their effects, is into bland or aseptic emboli and toxic or septic emboli.

Sources of emboli.—Emboli in the lungs come from the systemic veins, the right heart or the pulmonary artery; those in branches of the portal vein come from the radicles or trunk of this vein; those in systemic arteries from the pulmonary veins, the left heart, or some artery between the heart and the location of the embolus. Sources of aberrant emboli, resulting from unusual modes of transportation, will be considered subsequently (p. 231).

Various features in the structure and disposition of thrombi bearing upon the detachment of emboli have been described in the preceding article. Here may be especially recalled the continuation of an occluding venous thrombus in the form of a partly obstructing thrombus beyond the entrance of an important branch, and the occurrence of softening in the interior of older thrombi; phenomena evidently favourable to the detachment of fragments. Globular thrombi in the right heart, particularly in the auricular appendix, are a fruitful source of the emboli which cause pulmonary infarction in heart disease. Vegetations of the aortic and mitral valves, particularly of the latter, furnish the great majority of emboli in the aortic system. Thrombosis or embolism of an arterial trunk—as of the internal carotid, splenic, femoral—is often followed by the conveyance of fragments of the plug into branches of the artery. When the plug in the main trunk is an embolus, this secondary embolism is described by Cohnheim as "recurrent"—an epithet which has also been applied to retrograde embolism, and, therefore, to avoid confusion, had better not be used in either sense.

The detection of the source of an embolus is often unattended by any difficulty; but sometimes it requires prolonged and painstaking search, and occasionally even such a search is unrewarded. The greatest difficulties are encountered when the source is in some peripheral venous thrombus which has caused no symptoms and is unattended by lesions suggestive of its location. An entire thrombus may be dislocated and transported as an embolus.

Site of deposit.—Emboli are carried along by the blood-current until they are caught on some obstruction, or become lodged in a channel too narrow to permit their further passage. It is evident that embolism can scarcely occur except in the arterial system, pulmonary and systemic, and in branches of the portal vein. The rare instances of embolism of systemic veins will be considered under aberrant embolism (p. 231). An extremely rare occurrence, of which several instances are recorded, is the blocking of the tricuspid or mitral orifice by an embolus. The result is, of course, sudden death. Very often an embolus is caught at an arterial bifurcation, which it rides with a prolongation extending into each branch (riding embolus). This may happen where the diameter of each branch is greater than that of the embolus. It is not uncommon for several emboli to enter successively the same branch of the pulmonary artery.

Any artery open to the circulating blood may receive an embolus of appropriate size. The course followed by an embolus in its travels is determined by purely mechanical factors, of which the most important are the size, form, and weight of the plug; the direction, volume, and energy of the carrying blood-stream; the size of branches and the angles at which they are given off; and the position of the body and its members. In accord with these principles we find emboli in the lower lobes of the lungs oftener than in the upper; and in the right lung oftener than in the left, the right pulmonary artery being larger than the left. Emboli from the left heart are more frequently carried into the abdominal aorta and its branches than into the carotid or subclavian arteries. The left carotid, arising directly from the aortic arch at its highest point, is in more direct line with the aortic blood-stream than is the right carotid, and is therefore a commoner recipient of emboli. The left common iliac artery is also somewhat more directly in the line of the current in the abdominal aorta, and, therefore, receives emboli somewhat more frequently than the right.

The order of frequency in which emboli are found in the different arteries may be given about as follows:—pulmonary, renal, splenic, cerebral, iliac and the lower extremities, axillary and upper extremities, cœliac axis with its hepatic and gastric branches, central artery of the retina, superior mesenteric, inferior mesenteric, abdominal aorta, coronary of the heart. There is, however, considerable difference of statement on this point. As a matter of fact this list, like similar ones, does not inform us of the frequency with which the different arteries of the body receive emboli; for it is evident that it is based almost entirely upon embolic manifestations, and not upon the mere presence of emboli. If estimates of frequency be based only on infective emboli, the order would be in

several respects different, the hepatic artery, for example, standing higher in the list, and the cerebral lower—sufficient evidence that the customary data for determining the frequency of embolism in different arteries relate only to such emboli as leave behind some record of their presence. Infective emboli, however, do not inform us of the incidence of embolism in different arteries; for these produce abscesses or other lesions in certain special situations, and not in every place where they may lodge; a fact which is brought out clearly in the experimental injections of bacteria into the circulation of animals. It seems to me very probable that, of the systemic arteries, those going to the lower extremities must be more frequent receptacles of emboli than either the splenic or the renal; but the smaller plugs in the former usually leave no readily demonstrable record of their presence, whereas in the latter they always do.

Aberrant embolism.—Certain exceptions to the general rules already stated concerning the sources and direction of transportation of emboli may be grouped under the heading of aberrant or atypical embolism, the latter epithet being the one employed by Scheven to designate paradoxical embolism, and retrograde embolism.

Zahn gave the name "paradoxical embolism," and his assistant Rostan the name "crossed embolism," to the transportation of emboli derived from veins into the systemic arteries without passing through the pulmonary circulation. Cohnheim was the first to note the passage of venous emboli through an open foramen ovale into the aortic system; and since then there have been enough observations of this so-called paradoxical embolism to prove that, although not frequent, it is really of practical importance, and not merely a curiosity. Zahn and Rostan found an open foramen ovale in about one-fifth of their autopsies, which is a considerably smaller percentage than most pathologists, who have investigated the subject, have found. An opening in the form of an oblique slit is certainly very often present in the oval fossa (in 34 per cent of all cases according to Firket), and it has been demonstrated by actual observation that, under certain conditions, this form of opening suffices for the transit of emboli. In three cases an embolus was found by Zahn and Rostan actually engaged in the opening, and two or three similar observations have been made by others.

I have found records of twenty-eight cases of paradoxical embolism, and there is no reason to suppose that this list is complete. The evidence upon which the diagnosis is usually based is an open foramen ovale and the presence in the systemic arteries of coarse emboli, for which the only source to be found is on the venous side or in the right auricle. While in some of the cases there may be room for scepticism as to the venous origin of the arterial embolism, there can be none for Schmorl's observation, in a case of traumatic laceration of the liver, of plugs of hepatic tissue in the left auricle and the main trunk of the renal artery, with an open foramen ovale admitting a finger. Conditions favouring the occurrence of paradoxical embolism are, according to Zahn, increased pressure in the right auricle and lowered pressure in the left. Under these cir-

cumstanees the opening in the oval foramen is widened, and its walls bulge toward the left auricle. Rostan and Hauser have seen thrombi extending from the right auricle through the oval foramen into the left.

The best explanation of certain tumour metastases without pulmonary implication is by paradoxical embolism. Here, however, there is sometimes another possibility; for, as Zahn has demonstrated, tumour cells not of large size may pass through the pulmonary capillaries. Although the lungs are an excellent filter, their capillaries are certainly so wide that they may permit the transit of emboli too large to pass through capillaries elsewhere in the body.

The first conclusive observation of retrograde transport of an embolus in a human being was made by Heller, in 1870, who found, in a case of primary cancer of the cæcum and ileum, a loose plug of cancerous tissue in a branch of an hepatic vein. The only metastatic growths were in the mesenteric, retroperitoneal, and mediastinal lymphatic glands. Long before Heller, however, the conception of retrograde transport of venous emboli was familiar to pathologists; especially in the discussions of the explanation of metastatic hepatic abscesses in cases where the lungs are not involved and the atrium of infection does not communicate with the portal system. The experimental side of the subject was diligently cultivated. The general trend of opinion among pathologists, however, was opposed to the acceptance of the doctrine of retrograde transport, under conditions occurring in human beings, until the publication of von Recklinghausen's article on the subject in 1885. He reported a convincing observation of embolism of the renal veins with masses of sarcoma, derived from a primary growth of the tibia, and also of retrograde embolism from the left auricle into the pulmonary veins. Since this publication there have been a number of equally conclusive demonstrations of the retrograde transport of venous emboli, and the subject has been taken up again on the experimental side. Retrograde venous embolism is an interesting, but, so far as at present known, a rare occurrence.

The difficulty of making sure that a suspected thrombotic embolus in a systemic vein is not an autochthonous thrombus is doubtless the reason why most of the reports of retrograde transport relate to emboli of tumour-cells or parenchymatous cells. In addition to Heller's and von Recklinghausen's cases already mentioned, reference may be made to Arnold's observation of masses from a primary mammary carcinoma filling the superior longitudinal sinus, with invasion of the wall of the sinus from within by the new growth, but without any intracranial tumour outside of this wall; or indeed any metastasis elsewhere in the body except in the axillary and cervical lymph-glands: and also to Ernst's case of primary angio-sarcoma of the left kidney, growing into the renal vein, with a loose plug of sarcomatous tissue distending a branch of a coronary vein of the heart without connection with a metastatic growth. Bonome's observation of cancer of the thyroid with metastatic nodules in the liver, developing from plugs in the hepatic veins, should probably also be included in the list, as well as two cases of Bonome, reported by Lui,

in one of which a cancerous embolus secondary to cancer of the rectum was found in a branch of the superior mesenteric vein; and in the other a similar retrograde embolus, secondary to adeno-carcinoma of the liver, was met with in the right pampiniform plexus.

To Schmorl's and Lubarsch's cases of emboli of liver-cells in the cerebral and the renal veins may be added two observations from my laboratory, of which one has been reported by Flexner, of clumps of liver-cells in branches of the renal vein in cases with extensive hepatic necroses.

That retrograde transport of ordinary venous thrombi may occur, is demonstrated by Arnold's discovery in a large branch of an hepatic vein of a riding embolus identical in appearance with a thrombus which occupied the right ovarian vein and extended some distance into the inferior vena cava. Cohn accepted, for a limited class of cases, backward conveyance of venous emboli; and in this sense interprets an observation of thrombosis of the superior longitudinal sinus, with a plug in the right axillary vein identical in appearance with an undoubted embolus in the pulmonary artery. Von Recklinghausen has furnished evidence of the retrograde transport of infective emboli into the renal veins.

From these cases it is seen that retrograde embolism of particles of tumour, of tumour-cells, of parenchymatous cells, and of ordinary bland and infective thrombotic fragments has been observed. Experiments have demonstrated that, under certain conditions, light as well as heavy particles may be transported in the veins in a direction contrary to that of the normal blood-current. The veins in which retrograde embolism in human beings has been found are the hepatic, the renal, the mesenteric, the pampiniform plexus, the coronary of the heart, the cerebral veins and sinuses, the axillary and the pulmonary. Experimental retrograde embolism has been produced in many other veins, including those of the lower extremities. While venous valves, when intact, are undoubtedly a protection against this occurrence, they are often imperfectly developed or insufficient. Emboli have been repeatedly observed in the cerebral veins and sinuses which should be protected by valves in the jugular veins.

Retrograde embolism is usually explained by a temporary reflux of the venous current in consequence of some sudden obstacle to the return flow to the right heart, as may occur with forced expiration and coughing. Whatever increases the pressure in the veins near the heart, and impairs the assistance to the venous stream afforded by the respiratory movements and the suction of the right heart, favours this backward movement. Increased intrathoracic pressure, stenosis of the respiratory passages, spasm of respiratory muscles, distension of the right heart, tricuspid insufficiency, slowing of the heart's beats from vagus-irritation, are among the conditions believed to dispose to retrograde transport.

Ribbert does not accept the reflux theory of retrograde embolism; partly for lack of any positive observation of such backward flow beyond the immediate neighbourhood of the right heart, and partly on account of the difficulty in explaining what becomes of all the blood which would be momentarily pressed back toward the capillaries.

His explanation is that in conditions of high venous stasis, emboli, sticking loosely to the venous wall, are not moved forward by the feeble current, but are slowly pressed backward, step by step, by pulse-waves in the veins. For this view he finds support in experiments which he has made. Observations, partly experimental, of Arnold and of Ernst, cannot readily be reconciled with Ribbert's explanation; so that, notwithstanding difficulties needing further elucidation, the reflux theory seems at present the more probable for most cases.

Of a different nature from the preceding form of retrograde transport is the conveyance of emboli by a blood-current reversed from its normal direction in consequence of obstruction of veins by compression or other causes. This kind of retrograde transport from more or less permanent reversal of the normal current is far more frequent in lymphatic vessels than in veins, and plays an important part in the metastases of tumours by means of the lymphatics.

Anatomical characters.—The appearances observed in embolised vessels vary with the shape, size, consistence, and nature of the embolus, and the duration of its impaction. Approximately spherical emboli, as a rule, completely close the lumen of the artery in which they lodge. Cylindrical, elongated, or flat emboli are usually caught as riders at an arterial bifurcation; and often at first leave more or less of the channels by their side open. Thrombi several inches long may be washed out of the femoral or other peripheral vein. Such a transported thrombus may be found in the trunk or a primary division of the pulmonary artery, folded two, three, or even four times upon itself, and pressed at different points into several of the main arterial branches at the hilum of the lung, as in an interesting case described by Fagge. In this way an embolus may completely plug a vessel three or four times its diameter. Irregularly-shaped emboli, if of soft consistence, may be pressed into an artery so as to block the lumen completely; but if of firmer consistence they leave at first some space for the blood to flow. Emboli may be of such consistence as to be shattered by impact with the arterial wall, the fragments blocking many or all of the small branches, and producing the same effect as if the plug had been arrested in the main trunk.

An embolus is the starting-point of a secondary thrombus which usually, although not always, completes the closure of the vessel, if this was not effected by the embolus itself, and extends on each side to the nearest branch. The same metamorphoses and process of organisation, with consecutive changes in the vascular wall, occur with emboli and encapsulating thrombi, as described in the previous article for primary thrombi. Non-absorbable emboli or parts of emboli, like foreign bodies, are encapsulated by cells and tissue.

In cases of recent embolism, the plug can generally be recognised as an embolus without much difficulty; but, in those of long standing, the anatomical diagnosis between embolism and thrombosis may be difficult, or even impossible. The criteria for the recognition of a fresh embolus are for the most part sufficiently self-evident. Such a plug lies loosely or

is but slightly adherent to the vessel-wall. It often presents a broken or fractured surface which, in fortunate cases, may be made to fit on the corresponding surface of the thrombus from which it was originally broken off. It may be bent or folded, or show the marks of venous valves, or present ramifications which do not correspond to those of the artery in which it lies. It is of course of the first importance to find, if possible, the source of the embolus; and, when this is done, to make a careful comparison between the thrombus and the embolic fragment as to resemblances in structure and appearance.

After the embolus has become adherent and surrounded by a secondary thrombus, some of these differential criteria may still remain for a while; but, as time passes, the anatomical diagnosis becomes increasingly difficult. The embolus may perhaps still be distinguished from the surrounding thrombus by marked differences in its age and general appearance and structure, possibly by the presence of lime salts. An adherent plug which rides an arterial bifurcation is much more likely to be an embolus than a primary thrombus. In reaching a conclusion, weight must be given to the condition of the arterial wall; whether there be any local cause for thrombosis,—such as compression, aneurysm, arterio-sclerosis; and whether the microscope shows such secondary changes in the arterial wall as generally correspond to the apparent age and character of the adherent plug. The detection of a source for an embolus will be an important consideration. The clinical history may aid in the anatomical diagnosis; and all attendant circumstances, especially the existence elsewhere of undoubted emboli, should be taken into consideration. In some situations, as in branches of the renal or splenic arteries, primary thrombosis is so uncommon that the chances are all in favour of embolism.

It is evident from what has been said that in the older cases the anatomical diagnosis must often be based upon a weighing of probabilities, and that sometimes a positive conclusion cannot be reached.

Effects.—Bland or aseptic emboli produce chiefly mechanical effects referable to the obstruction to the circulation; toxic or septic emboli cause also other changes which may be described as chemical or infective. We shall consider first the mechanical effects.

The direct injury which may be inflicted upon the vessel wall by sharp calcareous emboli is, according to Ponfick, a rare cause of aneurysm. Embolic aneurysms, however, stand in much more definite relation to chemical properties of the embolus, as will be shown subsequently (p. 251).

Necrosis; Infarction.—The fate of a part supplied by an artery closed by a bland embolus depends altogether upon whether it is fed within a certain time after the obstruction with enough arterial blood to preserve its function and integrity. An embolus which does not completely plug the vessel may cause no appreciable interference with the circulation; but the closure of the lumen is usually soon effected by a secondary thrombus. The occlusion by a bland embolus of an artery with abundant anastomoses, such as those possessed by the arteries supplying bone, the voluntary muscles, the skin, the thyroid, the uterus,

usually causes no circulatory disturbance of any consequence. Even in these situations extensive multiple embolism, or embolism with extensive secondary thrombosis, may cause local anæmia with its consequences.

Sudden death may be the result of embolism of the trunk or a main division of the pulmonary artery, of one of the coronary arteries of the heart, or of the bulbar arteries.

If an adequate collateral circulation be not established within the proper time the inevitable fate of a part, supplied by an embolised artery, is degeneration or death. Local death is the regular result of embolism of branches of the splenic artery, the renal artery, the basal arteries of the brain, the central artery of the retina, and the main trunk of the superior mesenteric artery. It is the usual result of embolism of one of the coronary arteries of the heart, if the patient survive long enough; and it is the inconstant result, depending generally upon accessory circumstances, of embolism of the medium-sized and smaller branches of the pulmonary arteries, of cerebral arteries other than the basal, of the abdominal aorta, iliacs, main arteries of the extremities, and some other arteries. A collateral circulation may be established sufficiently to preserve the life of a part, but not to maintain its full nutrition; under these circumstances it undergoes fatty degeneration or simple atrophy.

When the dead part is so surrounded with living tissue that it can be permeated with lymph, as is usually the case in the viscera, the mode of death is that described by Weigert, and named by Cohnheim "coagulative necrosis." Here the dead protoplasm, and to some extent intercellular substances, undergo chemical changes, believed to be in part coagulative; and actual fibrillated fibrin may appear. If there be enough coagulable material present, the necrotic part becomes hard, dry, opaque, and somewhat swollen. For a time its general architecture, both gross and microscopic, is preserved; but the nuclei and specific granulations disappear early, the former largely by karyorrhexis.

An area of coagulative necrosis resulting from shutting off of the blood-supply is an infarct. Its shape corresponds to that of the arterial tree supplying it, and is, therefore, as a rule, approximately conical, or that of a wedge, the base being toward the periphery of the organ. The wedge-shape is most marked in smaller infarcts; large ones may be roundish or irregular in shape. The size depends upon that of the occluded artery. The colour is opaque, white, or yellowish, unless hæmorrhage is added to the necrosis. We thus distinguish anæmic, pale or white infarcts, and red or hæmorrhagic infarcts; but, in the latter no less than in the former, the essential thing is the coagulative necrosis, the hæmorrhage being merely something added to the necrosis. This was not always clearly recognised, it being supposed at one time that the hæmorrhage was the characteristic feature of infarcts, and that pale infarcts were simply decolourised hæmorrhagic infarcts. The name "infarct" (from *infarcire*, to stuff), like many other old medical terms, is therefore now used in a sense at variance with its etymological mean-

ing. In some situations, as the kidney and the retina, the infarct is nearly always pale; in others, as the lungs and the intestine, it is as constantly hæmorrhagic; and in yet others, as the spleen and the heart, it may be either white or red.

Where there is not a sufficient quantity of coagulable substance the area of coagulative necrosis does not become hard; and it may be of much softer consistence than normal, as is the case with the ischæmic necroses of the brain and spinal cord. Necrosis of peripheral parts, as the toes, foot, leg, hand, is not of the coagulative variety; for the dead part is not surrounded by living tissue to furnish the lymph which brings one of the factors essential for coagulation. This peripheral necrosis is called gangrene or mortification, and may be either dry or moist.

Collateral circulation; local anæmia.—As the state of the collateral circulation is the decisive factor in bland embolism, it becomes important to learn the conditions under which establishment or failure of this circulation occurs. This subject is one eminently open to experimental study; but more attention has been given to the anatomical than to the physiological side. In fact many writers seem to assume that the physiological factors can be so readily deduced from the laws of hydrodynamics that it is only necessary to investigate the size, arrangement, and distribution of the vascular tubes. Nevertheless experience has shown abundantly the danger of accepting anything in the physics of the circulation which has not been put to an experimental test on the living body. The experimental study of the physiological conditions which determine the development of a collateral circulation has demonstrated that this problem is by no means so simple as has been often represented; while some old errors have been corrected and new facts have been added, we are still far from an entirely satisfactory solution or any definite agreement of opinion. It is impossible here to do more than touch upon certain points bearing directly upon the subject in hand.

If an artery with slender anastomoses to its area of distribution, such as the femoral or the lingual in a frog's tongue, be tied, the immediate effect is stoppage of the circulation and anæmia of the part supplied by the occluded vessel, accompanied by contraction of the artery below the obstruction. Almost immediately, or within a short time, the blood begins to flow with greatly increased velocity through arteries arising above the point of ligation, but more rapidly only through those which send blood by anastomosing channels to the anæmic part. At the same time these arteries with quickened flow dilate. Formerly this vascular dilatation and increased flow were attributed to rise of blood-pressure above the ligature, but experiments have shown that in most situations this is a factor of relatively little moment. The rise of pressure cannot of course remain localised, and after ligation of the femoral artery amounts at most to only a few millimetres of mercury. Evidence of the relatively slight importance of this increased pressure is that the ligated artery actually contracts from the point of

ligation to the first branch arising above the ligature (Thoma, Goldenblum); and that the phenomena of dilatation and increased velocity occur only in arteries which send blood to the anæmic area, although others which carry blood elsewhere may arise nearer to the point of obstruction (Nothnagel). Moreover, it is hardly conceivable that increased pressure above the ligature can persist for the days and weeks which may be necessary for the full development of the collateral circulation.

As the increased flow cannot be due to any change in the viscosity of the blood, it must be due to increase of the pressure gradient. Therefore, if it is not the result in any marked degree of rise of pressure above the obstruction, it must be caused by lowered resistance to the stream in the anastomosing vessels. A moment's reflection will show that this is a far more purposeful and better mode of compensation than one brought about exclusively by a rise of pressure which must act upon arteries in no way concerned in the collateral circulation. The difficulty is an entirely satisfactory and complete explanation of the lowered resistance. It seems impossible that it can be due to anything but a widening of the bed of the stream. Von Recklinghausen has pointed out that the stream-bed for the anastomosing arteries is enlarged, inasmuch as after occlusion of the main artery the blood can flow from these collaterals not only in its original bed, but also, with diminished resistance, into the stream-bed belonging to the closed artery. The pressure gradient is thus increased, and consequently the velocity of the current is quickened in the anastomosing arteries. The cause of the dilatation of these arteries is not so clear. Thoma states as his first histo-mechanical principle that increased velocity of the blood-current leads to widening of the lumen, and eventually, if the increase continues, to growth of the vessel wall in superficies. Admitting this to be true, it can hardly be considered an explanation. As the collateral circulation develops perfectly, and with the same phenomena, after severance of all connection of the part with the central nervous system, it is evident that vaso-motor influences which are under central control are not essential to the process.

Satisfactory as von Recklinghausen's explanation is, as far as it goes, there is evidence that it does not cover all of the facts, and that there is also some mechanism by which the vessels of an ischæmic part are opened wide for the reception of the needed arterial blood. The existence of such a mechanism has been recognised by Lister, Cohnheim, Bier, and others. I must refer especially to the recent papers of Bier for a full presentation of the evidence on this point, and shall merely mention, as a familiar illustration, the extreme arterial hyperæmia which follows the removal of an Esmarch bandage. This flushing of a previously ischæmic part with arterial blood has been usually attributed to paralysis of vaso-constrictor or stimulation of vaso-dilator nerves, but Bier has shown that it occurs under conditions where this explanation can be probably excluded.

Without following Bier in his somewhat vitalistic conceptions, or speculating regarding the explanation of the phenomenon, we must, I think, admit that deprivation of arterial blood sets up some condition of a part whereby the vessels which feed it are in some way dilated to receive any fresh arterial blood which can reach them. The existence of such an admirably adaptive, self-regulatory capacity must be an important element in the development of a collateral circulation, and it may be remarked that it is a physiological rather than an anatomical factor. Bier believes that this capacity is very unequally developed in different parts of the body; being highest in external parts, and feeble or absent in most of the viscera. He is also of the opinion that the arterioles and capillaries of external parts have the power, by independent contractions, of driving blood into the veins; and that, by contraction of the small veins, the capillaries of these parts are in large measure protected from the reception of venous blood.

A possible, but I think not fully demonstrated, variation in the power to lower the resistance to the collateral stream of arterial blood is not, however, the only physiological property which influences the varying effects following obstruction to the arterial supply of different parts of the body. In some situations there are physiological arrangements which seem calculated to increase the difficulty of establishing an adequate collateral circulation. Mall has shown that contraction of the intestine exerts a marked influence upon the circulation through this organ. In the light of his results, it is interesting to note that, immediately after closure of the main trunk of the superior mesenteric artery of a dog, the intestine is thrown into violent tonic contractions and remains in an anæmic, contracted condition for two or three hours; after which the spasm relaxes and the bloodless condition at once gives place to venous hyperæmia and hæmorrhagic infarction, which appears in the third to sixth hour after the occlusion of the artery (Mall and Welch). This intestinal contraction, which under these circumstances is equivalent to arterial spasm, is probably one, although not the sole, reason why, in spite of free anastomoses, occlusion of the arteries supplying the intestine is followed by necrosis and hæmorrhage. That the explanation is not to be found simply in the great length of intestine supplied by a single artery, is evident from the fact that, if the extra-intestinal arteries supplying a loop much more than 5 centimetres in length be suddenly closed, the loop becomes hæmorrhagic and necrotic (Mall and Welch, Bier). That the conditions are essentially identical in man is proven by the experience of surgeons, who have repeatedly observed the same results after separation of the mesentery close to the intestine over about the same length. The blood can enter at each end of the short loop arteries, whose branches anastomose freely within the walls of the loop with those of the closed arteries; there being a particularly rich arterial plexus in the submucous coat (Heller). But these anastomoses are insufficient to preserve the part; although, with reference to the extent of territory to be supplied, they are large in comparison with some of

the trivial anastomoses which in external parts can respond effectively to the call for a collateral circulation to far larger areas. It must be left to future investigations to determine how far the inability of the intestinal vessels to compensate circulatory obstructions of a degree readily compensated in many other situations may be due, as claimed by Bier, to an inherent incapacity to lessen the resistance to the collateral stream, or to contraction of the muscular coats of the intestine, or to other causes. As Panski and Thoma have shown that slowing and interruption of the circulation in the spleen is followed, for several hours, by contraction of the muscular trabeculæ, it is probable that the development of a collateral circulation in this organ meets an obstacle similar to that in the intestine.

The various organs and tissues differ so widely as regards their susceptibility to the injurious effects of lack of arterial blood that local anæmias of equal intensity and duration may in one part of the body produce no appreciable effect, and in another cause the immediate abolition of function and the inevitable death of the part. In general, the more highly differentiated, specific cells of an organ are those which suffer first and most intensely. At one end of the scale are the ganglion cells of the brain, which, after the withdrawal of arterial blood for half an hour, and probably for a much shorter time, cannot be restored to life; and at the other end may be placed the periosteum, the cells of which may be still capable of producing bone two or three days after all circulation has ceased. So susceptible to local anæmia are the ganglion cells of the central nervous system, that not only is embolism of the branches of the cerebral arteries with only capillary communications, even of the minute terminal twigs in the cortex, always followed by necrotic softening, but also embolism of the anastomosing arteries in the pia very often causes softening of at least a part of the area supplied by the plugged artery. In the well-known Stenson experiment, temporary closure of the rabbit's abdominal aorta, just below the origin of the renal arteries, for an hour, results in the inevitable death of the ganglion cells in the central gray matter of the lumbar cord; and this notwithstanding the free anastomoses of the anterior and posterior spinal arteries. Many of the lesions which pass under the names of myelitis and hæmorrhagic encephalitis present the histological characters of ischæmic necrosis, although often no arterial occlusion can be found.

Perhaps, next to elements of the nervous system, the epithelial cells of the cortical tubules of the kidney are most susceptible to ischæmia. Litten has demonstrated that the temporary ligation of the renal artery of the rabbit for one and a half to two hours is followed invariably by necrosis of many of these epithelial cells. The cells in the walls of the blood-vessels and of connective tissue are relatively insusceptible to temporary slowing or cessation of the circulation.

It is evident from the preceding statements that the nature of the organ or tissue has a very important influence in determining whether local necrosis follows arterial embolism.

I have dwelt in some detail, although within the limited space necessarily inadequately, upon certain physiological characters of the circulation and of different organs and tissues, which appear to me deserving of more consideration than is usually given to them in discussions of the causes of embolic necroses and infarctions. It is, of course, not to be inferred that the number and size of the anastomoses are not of prime importance in determining the mechanical effects of arterial embolism, but, important as they are, they are not the exclusive determinants of the result. There is no single anatomical formula applicable to the circulatory conditions under which all embolic infarcts occur. The nearest approach to such a formula is that embodied in Cohnheim's doctrine of terminal arteries, a name which he gave to arteries whose branches do not communicate with each other or with those of other arteries, although capillaries are of course everywhere in communication with each other. Terminal vessels in this sense are the renal, the splenic, the pulmonary, the central artery of the retina, the basal arteries of the brain, and in general all branches of cerebral and spinal arteries after they have penetrated the brain or the spinal cord, the intramuscular branches of the coronary arteries of the heart, and the portal vein.[1] Cohnheim's teaching was that infarction occurs always after embolism of a terminal vessel, except of the pulmonary artery, whose capillaries, under ordinary conditions, are numerous and wide enough, after obliteration of an arterial branch, to maintain a sufficient circulation; and of the portal vein whose capillaries communicate freely with those of the hepatic artery. Thoma and Goldenblum have shown that, contrary to Cohnheim's results, no infarction follows embolism or ligature of the frog's lingual artery, which is or can readily be made a terminal artery, provided the tongue be replaced in the mouth after the operation so as to avoid stretching and drying from exposure to the air. It is, therefore, quite possible in some situations for an adequate circulation to be carried on through merely capillary communications, although the conditions are of course less favourable than when there are arterial anastomoses. On the other hand, as we have seen, embolism of anastomosing arteries, such as the mesenteric and the cerebral, may be followed by necrosis or infarction; and it cannot be said that the anastomoses in all of these cases are so unimportant that the arteries are virtually terminal.

We may conclude then that, under ordinary conditions, embolism of an artery having abundant and large anastomoses has no important

[1] There is some confusion as to the sense in which the words "terminal arteries" should be used, and it must be admitted that later investigations have detracted from the precision given to this term by Cohnheim. Thus some do not recognise the pulmonary artery as terminal, because the lung is supplied likewise by the bronchial and several other arteries whose capillaries communicate with those of the pulmonary artery. But unless we make the extent of a second arterial supply the decisive point in the definition, we should have, for the same reason, to exclude the renal and the splenic arteries from the class of "terminal arteries." Then the conception of arteries which are "functionally" but not anatomically terminal, creates still further confusion.

mechanical effect; that embolism of an artery with few and minute anastomoses, especially embolism of an artery with only capillary communications, is in many situations followed by necrosis, this result being favoured by certain physiological conditions which have been considered; and that embolism of arteries with fairly well-developed anastomoses may in certain situations also cause necrosis. Among the factors influencing the result, other than those relating to the number and size of the anastomoses, are the varying susceptibility of cells to ischæmia, interference with the circulation by contraction of muscular constituents of a part, and perhaps some inherent weakness in the physiological part of the mechanism by which a vigorous collateral circulation is established.

The compensation of sudden occlusion of an artery, by means of the collateral circulation, generally presupposes vessels with fairly normal walls and a certain vigour of the circulation. When the arteries have lost their elasticity, or the general circulation is feeble, or there is some pre-existing obstacle to the circulation such as chronic passive congestion, the development of an adequate collateral circulation is rendered correspondingly difficult, and may be impossible. Hence embolism of arteries of the extremities is often followed by gangrene in the aged, in arterio-sclerosis, in heart disease, and in infective, anæmic, and exhausting diseases. There are some observations which suggest that arterial spasm may co-operate with embolism in causing local anæmia.

The agencies by which a sufficient collateral circulation is established may be thrown out of order to such a degree that embolism of arteries having even the most ample anastomoses may be followed by necrosis. Foci of cerebral softening have been observed after occlusion of the internal carotid or of one of the vertebral arteries; although the circle of Willis, the largest and most perfect anastomosis in the body, was open, and no vascular obstruction could be found beyond it. Here, doubtless, an important factor in this exceptional occurrence is the rapidity with which nerve cells die when insufficiently fed with arterial blood. Cohn narrates the interesting case of a young woman rendered extremely anæmic by repeated hæmorrhages from cancer of the tongue. In order to control the bleeding the right carotid was tied. The patient immediately, to all appearances, lost consciousness; acquired ptosis of the right, then of the left eye, drawing of the angle of the mouth to the right, and relaxation and almost complete paralysis of the left extremities. The pulse almost disappeared and the face became very anæmic. Respiration was unaffected. The ligature was at once removed, and at the same moment the patient awoke "as from a dream," and the symptoms just mentioned quickly disappeared. She said that she had not completely lost consciousness but was unable to speak, and that her will had lost control over the organs. She had lost so much blood that she died three hours later without again losing consciousness before death. At the autopsy the carotids and all of the cerebral vessels were found open, and there was no change in the brain

except anæmia. In this case, the general anæmia was evidently so great that after closure of one carotid, which probably lasted not more than a minute or two, a sufficient supply of blood could not reach the brain through the circle of Willis.

Hæmorrhagic infarction.—The explanation of the accumulation and extravasation of blood in hæmorrhagic infarcts has been the subject of much speculation and experimental study. It is only in certain situations that infarcts are hæmorrhagic throughout; and, as already mentioned, these are no less necrotic than are the white infarcts. The necrosis and the hæmorrhage are co-ordinate effects of the disturbance of the circulation, neither being caused by the other. Virchow, in his early writings, suggested as possibilities, without definitely adopting any of them, most of the explanations which have since been advanced to account for the apparently paradoxical phenomenon that the occlusion of an artery may be followed by hyperæmia and hæmorrhage in the area of its distribution. Cohnheim, on the basis of experimental investigations published in 1872, came to the conclusion that the hyperæmia which may follow arterial embolism is the result of regurgitant flow from the veins, that the hæmorrhage occurs by diapedesis, and that this diapedesis is the result of some molecular change in the vascular walls deprived of their normal supply of nutriment. Although Cohn, in 1860, had shown conclusively, by numerous experiments on various organs, that the hyperæmia and hæmorrhage are not the result of regurgitant flow from the veins, Cohnheim's views were widely accepted until Litten, in 1880, in apparent ignorance of Cohn's work, repeated the experiments of the latter upon this point with the same results. The experiments of Dr. Mall and myself upon hæmorrhagic infarction of the intestine in 1887 convinced us that the blood which causes the infarct is not regurgitated from the veins. Cohnheim's results upon the frog as to the source of the blood in infarcts have not been confirmed by subsequent experimenters (Zielonko, Kossuchin, Küttner, Goldenblum, Thoma).

In situations where closure of an artery is followed by hæmorrhagic infarction, tying the veins also, so as to shut off all opportunity for reflux of venous blood, increases the hyperæmia and the hæmorrhage; and it may render an infarct hæmorrhagic which would otherwise be anæmic. On the other hand, if all vascular communication of a part be cut off except that with the veins, the part undergoes simple necrosis without hæmorrhagic infarction; and the result is the same even if the artery be cut open, so as to afford apparently the most favourable opportunity for backward flow from the veins. Or, expressed differently, if after closure of an artery all possibility of access of blood to the obstructed area through anastomosing arteries and capillaries be prevented, the veins remaining open, the part dies without hæmorrhagic infarction. Cohnheim was in error in supposing that hæmorrhagic infarction cannot occur where the veins are provided with valves, for it has been shown by Bryant, Köppe, and Mall that the small intestinal veins of the dog have effective valves; yet nowhere can hæmorrhagic

infarction be more readily produced experimentally by arterial obstruction than in the intestine of this animal. It is, then, quite certain that the blood which accumulates in the capillaries and small veins, and is extravasated in hæmorrhagic infarction, comes in through the capillary, and, if they exist, the arterial anastomoses, and is not regurgitated from the veins.

It cannot be doubted that the red corpuscles escape by diapedesis, not by rhexis; but our experiments are in entire accord with those of Litten in failing to furnish any support to the prevalent doctrine that the hæmorrhage is the result of changes in the walls of the vessels caused by insufficient supply of arterial blood; in fact they seem to us more conclusive upon this point. If a loop of intestine be completely shut off from the circulation for three or four hours (by which time, after ligation of the superior mesenteric artery, hæmorrhagic infarction begins to appear), and the obstruction be then removed, the blood at once shoots in from the arteries with great rapidity, and distends the vessels.[1] If, as usually happens, the blood has not coagulated in the vessels, no hæmorrhagic infarction subsequently appears. If, immediately after the circulation has been fully re-established in the loop, the superior mesenteric artery be ligated, the intestine from the lower part of the duodenum into the colon becomes the seat of hæmorrhagic infarction in the usual time; but the infarction does not appear earlier and is not more intense in the part which had been previously deprived of its circulation for three or four hours than in the rest of the small intestine. It is true, as Cohnheim has shown, that re-establishment of a local circulation, after its stoppage for many hours or days, may be followed by hæmorrhages in the previously ischæmic area; but hæmorrhagic infarction after arterial occlusion begins long before it is possible to demonstrate this change in the vascular wall caused by lack of blood-supply.

In a part undergoing hæmorrhagic infarction the circulation is greatly retarded in consequence of the small difference between the arterial and the venous pressures. This result may be brought about by rise of the venous or lowering of the arterial pressure. If the veins are obstructed sufficiently to render the outflow nil, or very small, and the arteries are open, the infarction is intense, and occurs with high intracapillary pressure. In consequence of the free anastomoses of veins this mode of production of an infarct is rare, but it may occur after thrombosis of the mesenteric, the splenic, and the central retinal veins. Its explanation offers no especial difficulties. If the veins are open the arterial pressure must be reduced in order to furnish the conditions necessary for the production of hæmorrhagic infarction. This latter case is the one present in arterial embolism with hæmorrhagic infarction, and is the one especially needing explanation. The intracapillary

[1] Bier's experimental results concerning the absence of hyperæmia after temporary ischæmia of the intestine do not, according to our experience, apply to prolonged ischæmia, which we found to be followed by intense hyperæmia.

pressure in this case may vary, but will generally be low. The arterial pressure is so low that the lateral pulse-waves nearly or entirely disappear, so that the force which drives the blood into the capillaries is no longer the normal intermittent one, which experiment has shown to be essential for the long-continued circulation of the blood through the capillaries and veins. This reduction, or absence of lateral pulsation, to which, so far as I know, other experimenters have not called attention, I believe to be the factor of first importance in the causation of hæmorrhagic infarction following arterial embolism.

We are not sufficiently informed concerning the physical and vital properties of the blood and of the blood-vessels to be able to predict positively what would happen under such abnormal circulatory conditions as those named, and actual observation only can furnish a solution. The difficulties in making such observations under the requisite conditions are considerable. Dr. Mall and I, in examining microscopically, in a specially constructed apparatus, the mesenteric circulation of the dog after ligation of the superior mesenteric artery, observed that immediately after the occlusion the circulation ceases in the arteries, capillaries, and veins. In a short time the circulation returns, but with altered characters. The arteries are contracted, but may subsequently dilate somewhat; and the blood from the collaterals flows through them with diminished rapidity, and without distinct lateral pulsation. The direction of the current is reversed in some of the arteries. The movement of the blood in the capillaries and veins is sluggish and irregular. The direction of the current in some of the veins may be temporarily reversed, but we were unable to trace a regurgitant venous flow into the capillaries. The distinction between axial and plasmatic current is obliterated. Gradually the smaller and then the larger veins become more and more distended with red corpuscles, and all of the phenomena of an intense venous hyperæmia appear, so that one instinctively searches for some obstruction to the venous outflow. The red corpuscles in the veins tend to accumulate in clumps, and may be moved forward, or forward and backward, in clumps or solid columns. Stasis appears in the veins. This is at first observed only here and there and is readily broken up by an advancing column of blood; but it gradually involves more and more of the veins, and in some becomes permanent, producing an evident obstacle to the forward movement of the blood. The same phenomena of distension with red corpuscles, clumping, to-and-fro movement, and stasis appear gradually in the capillaries. An interesting appearance, sometimes observed in capillaries and veins, is that of interrupted columns of compacted red corpuscles with intervening clear spaces which are sometimes clumps of white corpuscles, sometimes of platelets, sometimes only clear plasma. With the partial blocking of the veins and capillaries, red corpuscles begin to pass through the walls of these vessels by diapedesis; and after a time the hæmorrhage becomes so great that it is difficult to observe the condition within the vessels. The venous outflow is diminished

immediately or shortly after the closure of the superior mesenteric artery; it then rises, but later it continuously falls to a minimum.

An experiment which we made shows that the blood for hæmorrhagic infarction need not necessarily enter from the collaterals, and it sheds some light upon the condition of the circulation during the production of the infarct. We ligated all of the vascular communications of the intestine, with the exception of the main artery and vein, and then tied the intestine above and below, so that the included intestine was supplied only by the main artery and the blood returned by the main vein. Under these circumstances no infarction results. We then by a special device gradually constricted the main artery. In repeated experiments we found that not until the artery is sufficiently compressed to stop the lateral pulsations in its branches—the pressure in these being then about one-fifth of the normal—does hæmorrhagic infarction appear. Precautions were taken to make sure that the flow through the constricted main artery and its branches continued, and that the vein remained open. We have often measured the blood-pressure in branches of the superior mesenteric artery after ligation of this artery and during the progress of an infarction, and have found it to be generally one-fourth to one-fifth of the normal pressure. If the pressure on the arterial side falls below a certain minimum no hæmorrhage occurs in the infarction.

It is evident from the preceding description that the phenomena observed under these peculiar circulatory conditions are in large part dependent upon the physical properties of the blood, especially upon its viscosity and the presence of suspended particles which readily stick together; and differ in important respects from those which would occur under similar conditions with a thin, homogeneous fluid. The pressure gradient from arteries to veins of the ischæmic area is so low that the red corpuscles cannot fully overcome the resistance in the veins and capillaries. They accumulate in these situations, and probably undergo some physical change by which they become adherent to each other and to the vascular wall. The absence of the normal pulse-waves prevents the breaking up of these masses of corpuscles, the longitudinal pulse-waves sometimes observed having little or no effect in disintegrating the masses. In this way numerous small veins and capillaries become blocked, with a resulting rise of intracapillary pressure and diminution of outflow of blood through the veins. Von Frey has shown by interesting experiments that an intermittent pulsating force is necessary to prevent the speedy blocking of veins and capillaries with red corpuscles in carrying on artificial circulation with defibrinated blood through living organs. Kronecker has also demonstrated the influence of a pulsating force in increasing the venous outflow.

The diapedesis is due to the slowing and stagnation of the blood, and to the blood-pressure. Without a certain height of pressure there is no diapedesis; and, with a given retardation and stasis of the blood-current, the higher the intracapillary and intravenous pressure the

greater the amount of diapedesis. The matter which needs explanation is that the diapedesis may occur with lower than the normal pressure, and through vessel walls apparently unaltered. This I attribute to the fact that the red corpuscles, in consequence of the slow circulation, have opportunity to become engaged in the narrow paths followed by the lymph as it passes out between the endothelial cells. Diapedesis is a slow process, and the channels for it are much smaller than the thickness of a red corpuscle. Unless the red corpuscles can get started on the path between the endothelial cells, they cannot traverse it; and unless the circulation is very much slowed, and the outer plasmatic current obliterated, there is no opportunity for the corpuscles to become engaged between the endothelial cells, provided, that is, the vascular wall be normal. With greatly retarded circulation there is opportunity, and when the way in front is blocked by compact masses of red corpuscles, and sometimes by actual thrombi, the only path open to the corpuscles is that followed by the lymph between the endothelial cells. This then becomes the direction of least resistance for their movement.

The reason why infarctions are hæmorrhagic in some situations and not in others offers difficulties chiefly in consequence of our ignorance of the exact circulatory conditions which lead to the production of infarction in different parts of the body. It is generally assumed that these circulatory conditions are everywhere essentially the same; but this is by no means proven. As we have already seen, the physiological conditions which influence the result are various. It may be, therefore, that the requisite intracapillary and intravenous pressure, or some other condition of the circulation essential for the production of hæmorrhagic infarction, is lacking when the infarction is anæmic. In general a high venous pressure favours hæmorrhage in an infarction, and a low arterial pressure opposes it. The pressure in the superior mesenteric and portal veins is higher than in any other veins of the body. Hæmorrhagic infarction of the lung occurs especially with high degrees of chronic passive congestion in which the venous pressure is elevated. Thrombosis of veins seems to be the cause of at least some of the hæmorrhagic infarcts of the spleen. Hæmorrhagic infarction of the kidney may be produced experimentally by ligating the renal veins.

The studies of recent years upon the formation of lymph have demonstrated that the blood-vessels in different regions differ markedly in their permeability, those of the intestine being probably the most permeable. It may be that this difference in the constitution of the vessels is an important factor in determining the extent of diapedesis under similar circulatory conditions. As pointed out by Weigert, however, the greatest influence appears to be exercised by the resistance offered by the tissues to the escape of red corpuscles from the vessels. Hæmorrhagic infarction occurs especially where this tissue-resistance is low, as in the loose, spongy texture of the lungs, and in the soft mucosa and lax submucosa of the intestine. The hæmorrhage is far less in the dense muscular coats of the intestine. The considerable resistance offered

by the naturally firm consistence of the kidney is increased by the swelling and hardness resulting from coagulative necrosis of the epithelial and other cells of this organ; so that infarcts in this situation are nearly always anæmic in the greater part of their extent, although often hæmorrhagic in the periphery. The spleen is of softer consistence than the kidney; and here both white and red infarcts may occur, the latter especially with increased venous pressure. Although infarcts of the brain are soft, they are much swollen in the fresh state from infiltration with serum, so as to displace surrounding parts (Marchand). Here also there must be considerable resistance to the passage of red corpuscles through the vascular walls; but it is not uncommon for these softened areas to present scattered foci of hæmorrhage, and sometimes they are markedly hæmorrhagic. The intraocular pressure is probably a factor in making embolic infarcts of the retina anæmic. Embolism of arteries of the extremities with insufficient collateral circulation is often associated with extravasations of blood in the ischæmic areas.

Metamorphoses of infarcts.—A bland infarct is a foreign body most of the constituents of which are capable of absorption and replacement by connective tissue. The red corpuscles lose their colouring matter, some of which is transformed into amorphous or crystalline hæmatoidin. Polynuclear leucocytes, through chemiotactic influences, wander in from the periphery, the advance guard being usually the seat of marked nuclear fragmentation. This nuclear detritus mingles with that derived from the dead cells of the part. Granulation tissue develops from the living tissue around the infarct. Young mesoblastic cells wander in and assist the leucocytes in their phagocytic work. In the course of time the debris, which becomes extensively fatty, is disintegrated and removed; new vessels and new connective tissue grow in; and finally a scar, more or less pigmented according to the previous content of blood, marks the site of the infarct. In chronic endocarditis, depressed, wedge-shaped scars are often found in the spleen and the kidneys. They are rare in the lungs, not because hæmorrhagic infarcts in this situation usually undergo resolution like pneumonia or simple hæmorrhages, but because pulmonary infarcts generally occur under conditions not compatible with the prolonged survival of the patient. Partly organised infarcts are not uncommon in the lungs. In the brain, ischæmic softening may remain for a long time with apparently little change; but the common ultimate result is a cyst-like structure, which may be more or less pigmented, and is characterised by a meshwork of delicate neuroglia and connective-tissue fibres, infiltrated with milky or clear serum. Into the finer histological details of the process of substitution of an infarct by scar-tissue it is not necessary here to enter.

Chemical effects. Metastases.—Embolism and metastasis are sometimes employed as practically synonymous terms; but, in ordinary usage, by metastasis is understood any local, morbid condition produced by the transportation of pathological material by the lymphatic or blood-current from one part of the body to another.

We have already considered the coarser bland emboli in respect of their mechanical effects. Similar emboli, so small as to become lodged only in arterioles or capillaries, produce no mechanical effects unless, as rarely happens, numerous arterioles or capillaries are obstructed. The subject of transportation of pigment granules, and that of metallic and carbonifcrous dust, producing the various konioses, does not fall within the scope of this article. On account of certain special features, emboli of air, of fat, and of parenchyma-cells are most conveniently considered separately (pp. 254-259). There remain, in contrast to the dead and inert emboli to which our attention has been especially directed, those containing tumour-cells and parasitic organisms, or their products.

Masses of tumour growing into a blood-vessel may be broken off and transported as coarse emboli, producing all of the mechanical effects which we have described. There have been instances of sudden death from blocking of the pulmonary artery by cancerous or sarcomatous emboli, as in a case reported by Feltz. It is, however, as a cause of metastatic growths that emboli of tumour-cells have their chief significance. In individual cases it is oftener a matter of faith than of demonstration that the metastasis is due to such emboli, for opportunities to bring absolutely conclusive proof of this mode of origin of secondary tumours are not common. There have, however, been enough instances in which the demonstration has been rigorous to establish firmly the doctrine of the embolic origin of metastatic tumours. The evidence is that tumour-metastases are far more frequently due to capillary emboli than to those of larger size. Cancers and sarcomas furnish the great majority of emboli of this class; but in rare instances even benign tumours may penetrate blood-vessels and give rise to emboli, which exceptionally are the starting-points of secondary growths of the same nature as the primary. Mention has already been made of paradoxical and retrograde transport of tumour-emboli, as well as of the possibility of emboli of tumour-cells being so small as to traverse the pulmonary capillaries.

Certain animal parasites, as the Filaria sanguinis, Bilharzia hæmatobia, and Plasmodium malariæ, are inhabitants of the blood, or, in certain stages of their existence within the human body, are frequently found there. According to observations of Cerfontaine and Askanazy, the usual mode of transportation from the intestine of the embryos of Trichina is by the lymphatic and blood-currents. Echinococci have been known to pass from the liver through the vena cava; or primarily from the right heart into the pulmonary artery; and emboli from echinococci present in the wall of the left heart may be transported to distant organs (Davaine). The Amœba coli has been found in the intestinal veins; and, as stated by Dr. Lafleur in his article on "Amœbic Abscess of the Liver" (vol. v. p. 156), it is probable that this parasite can reach the liver through the portal vein.

On account of their frequency and serious consequences, infective emboli containing pathogenetic bacteria are of especial significance. Such

emboli constitute an important means of distribution of infective agents from primary foci of infection to distant parts of the body, where the pathogenetic micro-organisms, by their multiplication and their chemical products, can continue to manifest their specific activities. These emboli are often derived from infective venous thrombi connected with some primary area of infection. The portal of infection may be through the integument, the alimentary canal, the respiratory tract, the genito-urinary passages, the middle ear, or the eye, with corresponding infective thrombophlebitis in these various situations. Or there may be no demonstrable atrium of infection, as in many cases of infective endocarditis, which constitutes an important source of infective emboli. Emboli may of course come from secondary and subsequent foci of infection.

Coarse emboli are by no means essential for the causation of infective metastases, nor is it necessary that there should be any thrombosis to afford opportunity for the distribution of micro-organisms from a primary focus. Bacteria may gain access to the circulation, singly or in clumps; and such bacteria, without being enclosed in plugs of even capillary size, may become attached to the walls of capillaries and small vessels and produce local metastases. In this way infective material coming from the systemic veins may pass through the pulmonary capillaries without damage to the lungs, and become localised in various organs of the body.

We cannot explain the various localisations of infective processes in internal organs of the body exclusively by the mechanical distribution of pathogenetic micro-organisms by the circulation. We must reckon with the vital resistance of the tissues, which varies in different parts of the body, in different species and individuals, and with reference to different organisms. Even the pyogenetic micrococci, which are capable of causing abscesses anywhere in the body, do not generally produce their pathogenetic effects in every place where they may chance to lodge. They have their seats of preference, which vary in different species of animal and probably in different individuals.

The mere presence of pathogenetic bacteria in an embolus does not necessarily impart to it infective properties. This is true even of emboli containing pyogenetic cocci. I have in several instances observed in the spleen and kidney only the mechanical, bland effects of emboli derived from the vegetations of acute infective endocarditis, and have been able to demonstrate streptococci or other pathogenetic organisms in the original vegetations and in the emboli. As has already been remarked concerning thrombi, the line cannot be sharply drawn between bland emboli and septic emboli, simply on the basis of the presence of bacteria; although of course the septic properties must be derived from micro-organisms.

Infective emboli are capable of producing all of the mechanical effects of bland emboli; to these are added the specific effects of the micro-organisms or their products. These latter effects are essentially chemical in nature, and may occur wherever the emboli lodge, being

thus independent of the particular circulatory conditions essential for the production of mechanical effects. The most important of these chemical effects are hæmorrhages, usually of small size, and of an entirely different causation from those of hæmorrhagic infarction; necroses; inflammation, often suppurative, and, in case of putrefactive bacteria, gangrenous putrefaction. The most important function of infective embolism is in the causation of pyæmia. This subject has been most competently presented by Professor Cheyne in vol. i. p. 601, who has left nothing which requires further consideration here.

Embolic aneurysms.—Both the first recognition and the correct explanation of embolic aneurysms, at least of the great majority of cases, belong to British physicians and surgeons. Tufnell, in 1853, called attention to the influence of emboli in causing aneurysmal dilatation. There followed observations by Ogle, Wilks, Holmes, Church, and R. W. Smith, before the appearance, in 1873, of Ponfick's important paper on embolic aneurysms. Ponfick explained their formation by direct injury to the vessel-wall, inflicted usually by calcareous, spinous emboli; a view which has since been confirmed only by Thoma. In 1877, Goodhart, in reporting a case, gave the first satisfactory explanation of the mode of production of most of these aneurysms. He pointed out their association with acute infective endocarditis, and referred them to acute softening of the arterial wall, caused by toxic emboli. Other observations followed; and in 1885 Osler reported a case which, although not embolic, belongs etiologically to the same general category. This was a case of multiple mycotic aneurysms of the aorta due to infective endaortitis associated with infective endocarditis. In 1886 and 1887 appeared the contributions of Langton and Bowlby, the most valuable in English literature, who fully confirmed and expanded in detail the views first briefly announced by Goodhart. Eppinger, in his extensive monograph on aneurysms published in 1887, presented the results of a minute and careful study of this class of aneurysm, which he calls aneurysma mycotico-embolicum, and reported seven personal observations. Of later papers on the subject may be mentioned those of Pel and Spronck, Duckworth, Buday, and Clarke.

The evidence is conclusive that aneurysms may be caused by the destructive action of bacteria contained in emboli or directly implanted on the inner vascular wall. The usual source for such emboli in relation to aneurysm is furnished by acute infective endocarditis; but as there is every transition from ordinary warty endocarditis to the most malignant forms, and as the same species of micro-organisms may be found in the relatively benign as in the malignant cases, no single type of endocarditis is exclusively associated with these aneurysms. As is demonstrated by Osler's case, the same result may follow a mycotic endarteritis not secondary to embolism.

Eppinger has shown that at least the intima and the internal elastic lamella, and usually a part, sometimes the whole, of the media, are destroyed by the action of the bacteria, when an aneurysm is produced.

The site of the aneurysm corresponds to this circumscribed area of destruction, and therefore to the seat of the embolus, and is not above it, as some have supposed. The aneurysm is usually formed acutely, sometimes slowly. It may remain small or attain a large size. Multiplicity and location at or just above an arterial branching are common characteristics of embolic aneurysms. Favourite situations are the cerebral and mesenteric arteries and arterics of the extremities; but these aneurysms may occur in almost any artery. Arteries without firm support from the surrounding tissues offer the most favourable conditions for the production of embolic aneurysms.

Eppinger totally rejects direct mechanical injury from an embolus as a cause of aneurysm in the manner alleged by Ponfick; and Langton and Bowlby are likewise sceptical as to the validity of Ponfick's explanation beyond its possible application to some of his own cases. Certainly the great majority of embolic aneurysms are caused by pathogenetic organisms, and belong, therefore, to the class of parasitic aneurysms rather than to that of traumatic aneurysms. The affection is not a common one.

In this connection mere mention may be made of the interesting and very common verminous aneurysms of the anterior mesenteric artery of horses, caused by the Strongylus armatus.

General symptoms.—The symptoms of bland embolism are dependent mainly upon the degree and extent of the local anæmia produced by the arterial obstruction, and upon the specific functions of the part involved. In infective embolism there are additional symptoms referable to local and general infection. Here the constitutional symptoms usually overshadow those referable to the embolic obstruction and the local lesions.

It is not known that any symptoms attend the act of transportation of an embolus, even through the heart. In some situations there is sudden pain at the moment of impaction of the embolus (embolic ictus). This is more marked in large arteries, especially those supplying the extremities, than in smaller and visceral arteries. This pain has been attributed to various causes; but the most probable explanation seems to me to be irritation, by the impact of the embolus and by the sudden distension of the artery, of sensory nerves and nerve-endings in the vascular wall, present especially in the outer coat. It may be that the Pacinian corpuscles, which are particularly abundant in and around the adventitia of the abdominal aorta, the mesenteric arteries, the iliac and the femoral arteries, are susceptible to painful impressions. Embolism of the arteries named is characterised especially by the intensity of the pain, described sometimes as the sensation of a painful blow, at the moment of impaction of the embolus. Surgeons are familiar with the pain which attends the act of ligation of larger blood-vessels.

Of the pain which follows arterial embolism there are other causes, such as irritation of sensory nerves by local anæmia, altered tension of the part, presence of waste and abnormal metabolic products, structural

changes in nerves, inflammation of serous membranes covering infarcts, and so forth.

Some writers have spoken of the occasional occurrence of a nervous or reflex chill at the time of the embolic act; but, without denying the possibility of such an occurrence, I think that chills associated with embolism have been due usually to infection rather than to vascular plugging.

Although Stricker has constructed a hypothesis of fever based largely upon experiments interpreted by him as demonstrating that the commotion mechanically set up by emboli causes fever, I am not aware of any conclusive observations which show that fever may be produced in this way in human beings. Independently of the intervention of pathogenetic micro-organisms, arterial embolism may, however, be accompanied by elevation of temperature. Direct invasion of thermic nervous centres is, of course, only a special case in certain localisations of cerebral embolism. Gangolphe and Courmont attribute the fever sometimes observed after arterial occlusion to the absorption of pyretogenetic substances which they find produced in tissues undergoing necrobiosis. Other possible causes of fever may be the reactive and secondary inflammations consecutive to embolism.

Only in external parts, or parts open to inspection, can the phenomena of mortification, or "local cadaverisation," as Cruveilhier designated the results of shutting off arterial blood, be directly observed. Here are manifest the pallor accompanied by patches of lividity, the cessation of pulsation, the loss of turgidity, the coldness, the annihilation of function, the local death. The hæmorrhages which result from arterial obstruction may, however, be evident, not in external parts only, but also by the discharge of blood from the respiratory passages, the intestine, and the urinary tract; as the result of pulmonary, intestinal, and renal infarction respectively. The phenomena following retinal embolism are open to direct inspection by the ophthalmoscope. In parts not accessible to physical exploration the symptoms are referable mainly to the disturbance or abolition of function, and, therefore, vary with the special functions of the part. They will be considered in connection with embolism of special arteries (p. 261).

Diagnosis.—The main reliance in the differential diagnosis of embolism from thrombosis, or from other forms of arterial obstruction, is the discovery of a source for emboli, the sudden onset and the intensity of symptoms referable to local arterial anæmia, occasionally the disappearance or marked improvement of symptoms in consequence of complete or partial re-establishment of the circulation, and to some extent the absence of arterio-sclerosis or other causes of primary arterial thrombosis.

Valuable as these characters are for diagnosis, they are neither always present nor infallible. For pulmonary embolism the source is to be sought in peripheral venous thrombosis or cardiac disease with thrombi in the right heart; for embolism in the aortic system, the usual

source is the left heart, the great majority of cases being associated with disease of the aortic or mitral valves. It may, however, be impossible to detect the source, and its existence does not exclude the occurrence of thrombosis or other forms of arterial occlusion.

Nor are the symptoms consecutive to embolism always sudden in onset. An embolus may at first only partly obstruct the lumen of the vessel, which is later closed by a secondary thrombus; or it may be so situated that a thrombus springing from it is the real cause of the local anæmia. For example, an embolus lodged in the internal carotid artery usually causes no definite symptoms, but a secondary thrombus may extend from the embolus into the middle cerebral artery, in which case cerebral softening is sure to follow. On the other hand, the complete closure of an artery may be effected by a thrombus with such rapidity as to suggest embolism.

While the sudden occlusion of an artery by an embolus often causes temporary ischæmia of greater intensity and over a larger area than the more gradual closure of the same artery by a thrombus, so that when the collateral circulation is fully established the disappearance or reduction of the symptoms may be more marked in the former case than the latter, there may be even in thrombosis very decided improvement in the symptoms with the development of the collateral circulation.

The existence of arterio-sclerosis, of course, does not exclude embolism; but in case of doubt the chances are strongly in favour of embolism in children and young adults with healthy arteries, especially if cardiac disease be present; the most common association in the latter cases being with mitral affections.

Notwithstanding all of these uncertainties, the diagnosis of embolism, when it produces definite symptoms, can be correctly made in the majority of cases.

Air embolism.—The majority of cases in which death has been attributed to the entrance of air into the circulation have been surgical operations and wounds about the neck, shoulder, upper part of the thorax and skull, where air has been sucked into gaping veins and sinuses by thoracic aspiration; and cases in which air has entered the uterine veins, chiefly from the puerperal uterus, either spontaneously, as after abortions or detachment of placenta prævia, or after injections into the uterine cavity. Jürgensen has reported cases in which he believes death was caused by the entrance of gas into open veins connected with diseased areas in the stomach and intestine. Gaseous embolism has been assigned as the cause of symptoms and of death in caisson-disease and in divers; and it has been observed in connection with the development of gas-producing bacilli in the body.

A large number of experiments have been made to determine the effects of air introduced into the circulation. These have demonstrated that when the air is introduced slowly and at intervals, enormous quantities can sometimes be injected in a comparatively short time without

manifest injury. Thus Laborde and Muron injected into the external jugular vein of a dog 1120 cc. in the space of an hour and a half without causing death; and Jürgenson injected into the left femoral artery of a dog, weighing 43·5 kilo, 3550 cc. in the space of two hours and a half with only slight disturbance of the respiration and of the action of the heart. Under these circumstances the air-bubbles circulate with the blood, pass through the capillaries, and are speedily eliminated. Small amounts of air introduced directly into the carotids, the left heart or thoracic aorta, are often quickly fatal from embolism of the cerebral or coronary arteries.

The sudden introduction of large amounts of air into the veins is quickly fatal. Rabbits are much more susceptible to air embolism than dogs or horses. 50 cc. of air, and even more, can often be injected at once into the external jugular vein of a medium-sized dog without causing death; nor can a dog be killed by simple aspiration of air into the veins, even when an open glass tube is inserted into the axillary or jugular vein and shoved into the thorax (Feltz). Barthélemy says that as much as 4000 cc. of air must be introduced into the veins of horses in order to cause death.

After death from entrance of air into the veins, the right cavities of the heart are found distended with frothy blood, and blood containing air-bubbles is found in the veins—especially those near the heart, and in the pulmonary artery and its branches. It is exceptional under these circumstances for air to pass through the pulmonary capillaries into the left heart and aortic system.

There are two principal explanations of the cause of death in these cases. According to one, associated especially with Couty's name, the air is churned up with the blood into a frothy fluid in the right heart, and on account of its compressibility this mixture cannot be propelled by the right ventricle, which thus becomes over-distended and paralysed. According to another hypothesis, supported by experiments of Passet and of Hauer, blood mixed with air-bubbles is propelled into the pulmonary artery and its branches, but the frothy mixture cannot be driven through the pulmonary capillaries, so that death results from pulmonary embolism. The paralysing influence upon the heart of obstruction to the coronary circulation from accumulation of air in the right heart and in the coronary veins must also be an important factor, as well as the cerebral anæmia. Probably all of these factors—over-distension of the right heart, embolism of the pulmonary artery and its branches and of the coronary veins, and cerebral anæmia—may be concerned in causing death, although not necessarily all in equal degree in every case.

We have no information as to the amount of air required to cause death by intravenous aspiration or injection in human beings. It seems certain that man is relatively more susceptible in this respect than the dog or the horse; but it is probable that the fatal quantity of air must be at least several cubic centimetres, and that the entrance of a few bubbles of air into the veins is of no consequence. Many authors have entertained

very exaggerated ideas of the danger of entrance of a small quantity of air into the veins.

A large proportion of the cases reported in medical records as deaths due to air embolism will not stand rigid criticism. I have had occasion to look through the records of a large number of these cases, and have been amazed at the frequently unsatisfactory and meagre character of the evidence upon which was based the assumption that death was due to the entrance of air into the circulation.

So far as I am aware, the first attempt to make a bacteriological examination and to determine the nature of the gas-bubbles found in the blood under circumstances suggestive of death from entrance of air into the vessels, was made by me in 1891. A patient with an aortic aneurysm, which had perforated externally and given rise to repeated losses of blood, died suddenly without renewed hæmorrhage. At the autopsy, made in cool weather eight hours after death, there was abundant odourless gas in the heart and vessels without a trace of cadaveric decomposition anywhere in the body. It was proven that the gas was generated by an anaerobic bacillus, which was studied by Dr. Nuttall and myself, and named by us Bacillus aerogenes capsulatus. This bacillus is identical with one subsequently found by E. Fraenkel in gaseous phlegmons, and with that found by Ernst and others in livers which are the seat of post-mortem emphysema (Schaumleber). It is widely distributed in the outer world, being present especially in the soil, and often exists in the human intestinal canal. Dr. Flexner and I have reported twenty-three personal observations in which this gas-bacillus was found, and since our publication we have met with several additional ones. The only points concerning these cases which here concern us are, that this bacillus not only may produce gas in cadavers, but may invade the living body, and cause a variety of affections characterised by the presence of gas. There is evidence that the bacilli may be widely distributed by the circulation before death, and that gas generated by them may be present in the vessels during life. In most cases, however, in which this bacillus was present, the gas found in the heart and blood-vessels was generated after death. I do not consider that there is satisfactory evidence that similar effects may be produced by the colon bacillus, as has been asserted. There is, however, a facultative anaerobic bacillus, very closely allied to the B. aerogenes capsulatus, which may also cause gaseous phlegmons and produce gas in the vessels after death.

Our observations have demonstrated that the finding of gas-bubbles in the heart and vessels a few hours after death without any evidence of cadaveric decomposition is no proof that the gas is atmospheric air, or is not generated by a micro-organism. In all such cases a bacteriological examination is necessary to determine the origin of the gas. In many cases reported as death from entrance of air into the veins, the evidence for this conclusion has been nothing more than finding gas-bubbles in the heart and vessels after sudden or otherwise

unexplained death. In the absence of a bacteriological examination, the only cases which can be accepted as conclusive are those in which death has occurred immediately or shortly after the actually observed entrance of a considerable amount of air into the veins. There have been a number of carefully observed and indisputable instances in which during a surgical operation in the "dangerous region" life was imperilled or extinguished by the demonstrated entrance of air into wounded veins. After the audible sound of the suction of air into the vein, death was sometimes instantaneous; or it occurred in a few minutes after great dyspnœa, syncope, dilatation of the pupils, pallor or cyanosis, occasionally convulsions, sometimes the detection by auscultation over the heart of a churning sound synchronous with the cardiac systole, and the exit from the wounded vein of blood containing air-bubbles. These very alarming symptoms may disappear and the patient recover.

The evidence for this mode of death would seem to be almost as conclusive for a certain number of the sudden deaths following injections into the uterus, especially for the purpose of committing criminal abortion, and after the separation of placenta prævia. But I am sceptical as to this explanation of many of the deaths which have been reported as due to the entrance of air into the uterine veins. In the reports of Dr. Flexner and myself will be found the description of several cases of invasion of the B. aerogenes capsulatus, which without bacteriological examination would have the same claim to be regarded as deaths from entrance of air into the uterine veins as many of those so recorded. I have had the opportunity to examine the museum specimen of a uterus of a much-quoted case so reported, and I found in its walls bacilli morphologically identical with our gas-bacillus. Certainly all cases of this kind should hereafter be reported only after a bacteriological examination. Jürgensen's cases of supposed entrance of gas into the general circulation through the gastric and the intestinal veins are undoubtedly instances of invasion, either before or after death, of gas-forming bacilli.

Since Paul Bert's researches, the symptoms and death which occasionally follow the rapid reduction of previously heightened atmospheric pressure upon exit from a caisson or diver's apparatus, have been plausibly attributed to the liberation of bubbles of nitrogen in the circulating blood. This explanation of the phenomena is not, however, free from doubt, and it is difficult to bring conclusive evidence in its support in the case of human beings. Little weight can be attached at present to the reports of finding bubbles of gas in the blood-vessels of those who have died from caisson-disease, for these reports have not hitherto been accompanied by any bacteriological examination to determine the source of the gas.

Ewald and Kobert have made the curious observation that the lungs are not air-tight under an increase of intrapulmonary pressure which may temporarily occur in human beings. They found in experiments on animals that small air-bubbles may appear under these circumstances

in the pulmonary veins and left heart without any demonstrable rupture of the pulmonary tissue; and they argue that this may occur under similar conditions in human beings. The entrance into the circulation of a few minute air-bubbles in this way would doubtless produce no effects. Ewald and Kobert cite two or three not at all convincing published cases in support of the possibility of death resulting from the entrance of air through unruptured pulmonary veins. Very plausible is Janeway's hypothesis that the transitory hemiplegia and other cerebral symptoms, which have occasionally been observed to follow washing-out the pleural cavity with peroxide of hydrogen, or some other procedure by which air or gas may accumulate in this cavity under high pressure, are due to air embolism or gaseous embolism of the cerebral vessels.

Not less remarkable are the experimental observations of Lewin and Goldschmidt concerning air-embolism following injections of air into the bladder and its passage into the ureters and renal pelves. It has not been demonstrated that the same phenomenon can occur under similar conditions in human beings.

Fat embolism.—Fat embolism, first observed in human beings by Zenker and by Wagner in 1862, is the most common form of embolism; but its practical importance does not correspond to its frequency. It is of greater surgical than medical interest, inasmuch as the severer forms are nearly always the result of traumatism. The usual conditions for its occurrence are (i.) rupture of the wall of a vessel, (ii.) proximity of liquid fat, and (iii.) some force sufficient to propel the fat into the vessel.

Fat-embolism probably occurs in every case of fracture of bone containing fat-marrow. When the bone is rarefied, and contains an unusual quantity of fat-marrow, embolism resulting from its injury may be very extensive; as is illustrated by several fatal cases of fat-embolism following the forcible rupture of adhesions in an anchylosed joint. Ribbert has shown that fat-embolism may result from simple concussion of bone, as from falls or a blow. Inflammations, hæmorrhages and degenerations of the osseous marrow may cause it. It may likewise result from traumatic lesions, necroses, hæmorrhages, inflammation of adipose tissue in any part of the body,—of the brain, of a fatty liver, in a word of any organ or part containing fat. Injury to the pelvic fat during childbirth leads to fat-embolism. Oil-globules in the blood may come from fatty metamorphoses of thrombi, of endothelial cells and of atheromatous plaques. The lipæmia of digestion and of diabetes mellitus has not been generally supposed to lead to fat-embolism, but Sanders and Hamilton have observed capillaries filled with oil-globules after death from diabetic coma, and they attribute in certain cases dyspnœa and coma in diabetes to this cause.

In the great majority of cases, fat-embolism is entirely innocuous, and, unless it is searched for, its existence is not revealed at autopsy, and then only by microscopical examination. Plugging of capillaries and small arteries with oil may, however, be so extensive and so situated as to cause grave symptoms and even death. More moderate plugging

may aid in causing death in those greatly weakened by shock, hæmorrhage, or other causes. The detection of fat-embolism in the pulmonary vessels may be of medico-legal value in determining whether injuries have been inflicted before or after death.

The deposition of fat-emboli is most abundant in the small arteries and capillaries of the lung, where in extreme cases the appearances of microscopic sections may indicate that considerably over one-half of the pulmonary capillaries are filled with cylinders and drops of oil. In rare instances of extensive injury the amount of fat in the blood may be enormous, so that post-mortem clots in the heart and pulmonary artery may be enveloped in layers of solidified fat. Some of the oil passes through the pulmonary capillaries and blocks the capillaries and arterioles of various organs; those which suffer most being the brain, the kidneys, and the heart. The extent of the embolism in the aortic system varies much in different cases, being sometimes slight, at other times extensive. Probably the force of the circulation determines the amount of fat which passes through the pulmonary capillaries. Oil once deposited may be again mobilised and transferred to other capillaries.

As already stated, it is only in the comparatively rare instances of extensive fat-embolism that effects of any consequence are produced. The fat itself is perfectly bland and unirritating, although it may be accidentally associated with toxic or infective material. The lesions and symptoms, when present, are referable mainly to the lungs, the brain, the heart, and the kidneys. These lesions are multiple ecchymoses (which in the lungs and the brain may be very numerous and extensive), pulmonary œdema, and patchy fatty degeneration of the cardiac muscle and of the epithelium of the convoluted tubules of the kidney. Pulmonary œdema, referable probably to paralysis of the left heart, is common with extensive fat embolism of the lungs. Death may undoubtedly be caused by fat-embolism of the cerebral vessels, possibly also by that of the coronary vessels.

The *symptoms* in the extreme cases are quickened respiration, rapid prostration, reddish frothy expectoration, the crepitations of pulmonary œdema, small frequent pulse, cyanosis, and—with cerebral invasion—coma, vomiting, convulsions, and occasionally focal cerebral symptoms. The temperature may either fall or rise. Oil-globules are often found in the urine, but it is still an open question whether these are eliminated through the glomerular capillaries, many of which are often filled with oil.

From the recent investigations of Beneke it appears that the oil is readily disposed of, in small part by saponification, possibly oxidation, and emulsion by means of the blood plasma; but in larger part through the metabolic and phagocytic activities of wandering cells which form a layer around the fat. The saponifying ferment — lipase — which Hanriot has discovered in blood-serum is probably one of the agents concerned in disposing of the fat.

Embolism by parenchymatous cells.—This is in general of more

pathologico-anatomical than clinical interest, and therefore need not be considered here in detail. As has been shown by Lubarsch, Aschoff, and Maximow, bone-marrow cells, with large budding nuclei, usually undergoing degeneration, may often be found lodged in the pulmonary capillaries after injury to bone, in toxic and infective diseases, in leucocythæmia, and in association with emboli of other parenchymatous cells. I have seen them in large number in capillaries of the liver in a case of spleno-medullary leucocythæmia.

Next in frequency are emboli of liver-cells, which are found chiefly in pulmonary capillaries, but may pass through an open foramen ovale so as to reach capillaries of the brain, kidneys, and other organs. F. C. Turner in 1884 first observed liver-cells within hepatic vessels; and later Jürgens, Klebs, Schmorl, Lubarsch, Flexner, and others noted their transportation as emboli after injury, hæmorrhages, and necroses of the liver, and with especial frequency in puerperal eclampsia. Secondary platelet-thrombi are usually formed about the cells.

Especial significance was attached by Schmorl to the presence of emboli of placental giant-cells (syncytium) in the pulmonary capillaries in cases of puerperal eclampsia; but these emboli, although frequent, are not constant in this affection, and they may occur in pregnant women without eclampsia (Lubarsch, Leusden, Kassjanow).

To the group of parenchymatous emboli may be added the transport of large cells from the spleen to the liver through the splenic and portal veins. I have seen large splenic cells containing pigment and parasites blocking the capillaries of the liver in cases of malaria; and also the well-known large splenic cells containing red blood-corpuscles in cases of malaria and of typhoid fever. The crescentic endothelial cells of the spleen may enter the circulation.

After traumatism and parenchymatous embolism fragments of osseous and medullary tissue may be carried to the pulmonary vessels as emboli (Lubarsch, Maximow). Emboli of large masses of hepatic tissue have been found in branches of the pulmonary artery by Schmorl, Zenker, Hess, and Gaylord as a result of traumatic laceration of the liver. Chorion-villi may be detached and very rarely conveyed as emboli to the lungs (Schmorl), or by retrograde transport to veins in the vaginal wall (Neumann, Pick). This is much more likely to occur from chorionic carcinoma and moles than from a normal placenta.

So far as known, emboli of marrow-cells, of liver-cells, of normal syncytial cells, and of splenic cells undergo only regressive metamorphoses, which lead to their eventual disappearance. The possibility that without the presence of any syncytial tumour in the uterus or tubes, emboli of syncytial cells may give rise to malignant tumours with the typical structure of those developing from syncytium, seems to have been demonstrated by a case reported by Schmorl; but it can hardly be supposed that the displaced syncytial cells were normal. Emboli of liver-cells manifest a distinct coagulative influence (Hanau, Lubarsch); and in two instances Lubarsch attributed infarcts in the kidney and the

liver to thrombi formed around these cells. Marrow-cells and syncytial cells may likewise cause, in less degree, secondary platelet and hyaline thrombi; but it does not appear that these thrombi have the importance in the etiology of puerperal eclampsia which is attached to them by Schmorl. With a few exceptions, no important lesions of the tissues or definite symptoms have been conclusively referred to emboli of these parenchymatous cells.

Although widely different in results, the transportation of tumour cells by the blood-current is a process similar to that of parenchymatous embolism, for which indeed cellular embolism seems to me a preferable designation. Benno Schmidt has found small branches of the pulmonary artery plugged with cancer-cells derived from gastric cancer or its metastases, both with and without growth of the cells into the walls of the plugged arteries. Such cells may reach the lungs by conveyance through the thoracic duct and innominate vein.

Embolism of special arteries.—I shall present the salient characteristics of the more important special localisations of embolism, so far as these have not been sufficiently considered in the preceding pages, or do not pertain to other articles in this work. Embolism of the central nervous system will be discussed in the next volume under Diseases of the Brain and Spinal Cord. The pyæmic manifestations of infective embolism have been described in the articles on "Pyæmia" (vol. i. p. 601) and on "Infective Endocarditis" (vol. i. p. 626 and vol. v. p. 876).

Pulmonary embolism.—The effects of pulmonary embolism vary with the size of the plugged vessel, the rapidity and completeness of its closure, the nature of the embolus, and associated conditions. Embolism of large, of medium-sized and small arteries, and of capillaries may be distinguished.

The most frequent source of large emboli is peripheral venous thrombosis, although they may come from the right heart. Sudden or rapid death follows embolism of the trunk or of both main divisions of the pulmonary artery. It may occur also from embolism of only one of the main divisions or from plugging of a large number of branches at the hilum of the lung.

Death may be instantaneous from syncope. More frequently the patient cries out, is seized with extreme precordial distress and violent suffocation, and dies in a few seconds or minutes. Or, when there is still some passage for the blood, the symptoms may be prolonged for hours or even days before the fatal termination. The symptoms of large pulmonary embolism are the sudden appearance of a painful sense of oppression in the chest, rapid respiration, intense dyspnœa, pallor followed by cyanosis, turgidity of the cervical veins, exophthalmos, dilatation of the pupils, tumultuous or weak and irregular heart's action, small, empty radial pulse, great restlessness, cold sweat, chills, syncope, opisthotonos, and convulsions. The intelligence may be preserved, or there may be delirium, coma, and other cerebral symptoms. Particularly striking is the contrast between the violence of the dyspnœa and the

freedom with which the air enters the lungs and the absence of pulmonary physical signs; unless in the more prolonged cases it be the signs of œdema of the lungs. Litten found in two cases systolic or systolic and diastolic stenotic murmurs in the first and second intercostal spaces on the right or left side of the sternum. In prolonged cases the symptoms may be paroxysmal with marked remissions. Recovery may follow after the appearance of grave symptoms. There has been much and rather profitless discussion as to the degrees in which the symptoms are referable to asphyxia, to cerebral anæmia, or to interference with the coronary circulation. Doubtless all three factors are concerned, but the exact apportionment to each of its due share in the result is not easy, nor very important.

The diagnosis is based upon the sudden appearance of the symptoms, with a recognised source for an embolus. It is surprising to find in the larger statistics, as those of Bang and of Bunger, how often the thrombosis leading to fatal pulmonary embolism has been latent. Here the diagnosis cannot always be made; but in many cases it may be suspected, or be reasonably certain: as when the above-mentioned symptoms appear in puerperal women; during convalescence from infective fevers, as enteric fever, influenza, pneumonia; in marasmic and anæmic conditions, as phthisis, cancer, chlorosis; after surgical operations, especially those involving the pelvic organs; and in persons with varicose veins.

Even at autopsies the source for the embolus has sometimes been missed, but this has been due generally to inability or failure to make the necessary dissection of the peripheral veins, or to dislocation of the entire thrombus. Serre has published a series of cases of pulmonary embolism with latent thrombosis, showing the difficulties which may attend the discovery of the source, and the frequency with which patient search reveals the primary thrombus. The majority of plugs in the trunk or main divisions of the pulmonary artery, found in cases of sudden death, present the anatomical characters of emboli, associated perhaps with secondary thrombi; but there remain a certain number of cases of sudden or gradual death from primary thrombosis of the pulmonary artery, or from thrombosis extending into a main division from an embolus in a smaller branch (see Thrombosis, p. 208).

Bland embolism of medium-sized and small branches of the pulmonary artery in normal lungs, and without serious impairment of the pulmonary circulation, usually causes no symptoms and no changes in the parenchyma of the lungs. Even in lungs structurally altered, and with serious disturbances of the circulation, such embolism may be without effects. The explanation of the harmlessness of the majority of medium-sized and small pulmonary emboli is that the collateral circulation through the numerous and wide pulmonary capillaries is, under ordinary conditions, quite capable of supplying sufficient blood to an area whose artery is obstructed, to preserve its function and integrity; and that the pulmonary tissue, in contrast to the brain and the kidney, is relatively insusceptible to partial local anæmia.

Often enough, however, medium-sized and smaller branches of the pulmonary artery are occluded by emboli or thrombi under conditions where the pulmonary circulation is incapable of compensating the obstruction, and then the result is hæmorrhagic infarction of the lung. The most common and important of the conditions thus favouring the production of hæmorrhagic infarction is chronic passive congestion of the lungs from valvular or other disease of the left heart. It is especially during broken compensation of cardiac disease that hæmorrhagic infarction of the lungs occurs, sometimes indeed almost as a terminal event. Other favouring conditions are weakness of the right heart, fatty degeneration of the heart, general feebleness of the circulation, pulmonary emphysema, infective diseases.

The source of the embolus causing pulmonary hæmorrhagic infarction is oftener the right heart than a peripheral thrombus. Globular thrombi are often formed in the right auricular appendix and ventricular apex in uncompensated disease of the left heart, particularly of the mitral valve (see Thrombosis, p. 183). The infarction may be caused also by thrombosis of branches of the pulmonary artery, which are not infrequently the seat of fatty degeneration of the intima and of sclerosis in cardiac disease and in emphysema. Thrombi in larger branches often give rise to emboli in smaller ones.

Pulmonary infarcts are usually multiple, more frequent in the lower than the upper lobes, and occur on the right side somewhat oftener than on the left; corresponding thus with the distribution of emboli. Their size varies generally from that of a hazel-nut to a pigeon's egg; but it may be smaller or much larger, up to half or even an entire lobe. They are conical or of a wedge-shape, the base being at the pleura. Infarcts are rarely buried in the substance of the lung so as to be invisible from the pleural surface. Typical fresh infarcts are strikingly hard, sharply circumscribed, swollen, upon section dark red, almost black, smooth or slightly granular, and much drier than ordinary hæmorrhages. Examined microscopically, the air-cells, bronchi, and any loose connective tissue which may be included in the infarct are stuffed full of red corpuscles. The capillaries are distended, and in all but the freshest infarcts usually contain, in larger or smaller amount, hyaline thrombi, to which von Recklinghausen attaches much importance in the production of the infarct. Fibrin may be scanty in very recent infarcts, but in older ones it is abundant. The walls of the alveoli in the central part of the infarct are the seat of typical coagulative necrosis with fragmentation and solution of the nuclear chromatin. It is probable that the red corpuscles also undergo some kind of coagulative change, for otherwise it is difficult to explain the extremely hard consistence of the fresh infarct. It is possible that small pulmonary infarcts and very recent ones may occur without necrosis; but the ordinary ones are necrotic, and cannot therefore be removed by resolution; but, if the patient lives long enough and suppuration or gangrene of the infarct does not ensue, are substituted by cicatricial tissue (Willgerodt).

Ever since the first admirable description of hæmorrhagic infarcts of the lung by Laennec there has been considerable difference of opinion as to their explanation. The doctrine that they are usually caused by emboli, however, gradually gained general acceptance. This explanation has always had opponents, chiefly on the grounds that emboli often occur in the pulmonary arteries without infarction; that infarction is not always associated with obstruction of the corresponding artery; that some have believed that simple hæmorrhages may produce the same appearances, and that until recently attempts to produce pulmonary infarction experimentally have been without positive or at least sufficiently satisfactory results. Hamilton is strongly opposed to the embolic explanation, and attributes hæmorrhagic infarction of the lung to a simple apoplexy, resulting usually from rupture of the alveolar capillaries in chronic passive congestion. Grawitz, likewise, considers that embolism has nothing to do with the causation of pulmonary infarction, which he explains by hæmorrhage from newly-formed, richly-vascularised, peribronchial, subpleural, and interlobular connective tissue consecutive to the chronic bronchitis of cardiac and other diseases. He emphasises structural changes in the lung as an essential pre-requisite for infarction. Grawitz's attack especially has stimulated investigation which, in my opinion, has strengthened the supports of the embolic doctrine of hæmorrhagic infarction.

The evidence seems to me conclusive that pulmonary infarcts are caused by embolism and thrombosis of branches of the pulmonary artery. In the great majority of cases the arteries supplying the areas of infarction are plugged. Upon this point my experience is in accord with that of von Recklinghausen, Orth, Hanau, Oestreich, and many others. That these arterial plugs are secondary to the infarction is improbable, as hæmorrhages elsewhere, as well as undoubted ones in the lungs, often as they cause secondary venous thrombosis, rarely cause arterial thrombosis. Moreover, there is sometimes an interval of open artery between the plug and the infarct, a relation not observed with the undoubtedly secondary thrombosis of veins connected with the infarct, and not explicable on the assumption that the arterial thrombosis is secondary. The plug often has the characters of a riding embolus. Not a few of the plugs, however, are primary thrombi. The occasional occurrence of pulmonary infarction without obstruction in the arteries has as much, but no more, weight against the embolic explanation as the similar, and I believe quite as frequent, occurrence of splenic infarcts without embolism or thrombosis of the splenic arteries. Both the hæmorrhage and the necrosis of infarcts are essentially capillary phenomena, each being independent of the other; and undoubtedly can occur, in ways little understood, in various regions, without plugging of the arteries.

The anatomical characters of pulmonary infarcts are essentially the same as those of hæmorrhagic infarcts of the spleen and other parts. The conical shape, the hard consistence, the peripheral situation, the coagulative necrosis are distinctive characters of pulmonary as of splenic

infarcts. The necrosis cannot well be attributed to compression of the alveolar walls by the extravasated blood, for the capillaries in these are usually distended widely with blood. It has the general characters of the ischæmic necrosis of infarcts, except that it apparently occurs somewhat later in the formation of the infarct and does not usually reach the periphery; phenomena which may be explained by the relative tolerance of the pulmonary tissue of partial ischæmia, and by a better peripheral circulation than is present in infarcts elsewhere.

Inasmuch as emboli do not ordinarily cause infarction in normal human lungs with vigorous circulation, it is not surprising to find that similar emboli under similar conditions do not cause infarction in the lungs of animals. It is not easy to reproduce experimentally in animals the conditions under which pulmonary infarcts occur in man; yet there have been several valuable contributions in recent years to the experimental production of pulmonary infarction: these have furnished an experimental basis, which, if not all that is to be desired, still marks a distinct advance for the embolic doctrine of hæmorrhagic infarction of the lung. Pulmonary infarcts, in all essential respects identical with those in human lungs, have been produced by experimental embolism or arterial occlusion by Cohnheim and Litten, Perl, Küttner, Mögling, Grawitz, Klebs, Gsell, Sgambati, Orth, Zahn, and Fujinami. Most of these experimental infarcts have been produced under conditions not very analogous to those of human infarcts; but the essential fact that typical hæmorrhagic infarction of the lung may be caused by arterial plugging has been experimentally established. Into the details of these experiments it is impossible here to enter.

Whether genuine hæmorrhagic infarcts of the lung may ever be caused by simple hæmorrhage from rupture of blood-vessels is perhaps an open question. At present this mode of their production seems to me undemonstrated and improbable, so that I hold that simple pulmonary apoplexies and genuine infarcts should be clearly distinguished from each other. Neither the results of experimental introduction of blood into the trachea (Perl and Lippmann, Sommerbrodt, Nothnagel, Gluziński), nor the appearances of the lungs after undoubted bronchorrhagias, pneumorrhagias, and suicidal cutting of the trachea support the opinion that aspiration of blood from the trachea and bronchi causes genuine hæmorrhagic infarction. In only one of Sommerbrodt's numerous experiments was such infarction observed, and this he regards as accidental. The explanation of this exceptional result is probably the same as in Perl's experiment with thrombosis after venesection and anæmia.

I have seen, in two or three instances, nearly white or pale-red fresh anæmic infarcts in densely consolidated lungs.[1] Even when caused by bland emboli pulmonary infarcts are exposed to the invasion of bacteria from the air-passages; and such bacterial invasion may lead to sup-

[1] In very rare instances pulmonary infarcts are anæmic in consequence of extreme weakness of the circulation (87).

puration or gangrene. Completely cicatrised pulmonary infarcts occur, but they are not common—life being usually cut short by the associated cardiac disease before the infarct is healed.

Hæmorrhagic infarction of the lungs may be entirely latent; often, however, the diagnosis can be made during life. The affection may be ushered in by a chill or chilly sensation, increase of a usually existing dyspnœa, and localised pain in the side. These symptoms are far from constant. The characteristic symptom, although by no means pathognomonic, is bloody expectoration. Profuse hæmoptysis was noted by Laennec, but is very rare. The sputum contains dots and streaks of blood, or small dark coagula; or, more frequently, the blood is intimately mixed with the expectoration, which is in small masses and usually less viscid and darker red than that of pneumonia, although it may resemble the latter. Blood may be present in the sputum for one or two weeks or even longer after the onset of the infarction. It acquires after a time a brownish-red tint, and generally contains the pigmented epithelial cells usually seen in the sputum of chronic passive congestion. Circumscribed sero-fibrinous pleurisy is usually associated with pulmonary infarction. Even with infarcts not more than four or five centimetres in diameter the physical signs of consolidation and subcrepitant râles can sometimes be detected; usually in the posterior, lower parts of the lungs. These signs are referable not only to the infarct, but also to the surrounding localised œdema and perhaps reactive pneumonia. There may be moderate elevation of temperature. When the characteristic bloody expectoration, together with signs of circumscribed consolidation, appears in the later stages of cardiac disease, or with peripheral venous thrombosis, there is generally little doubt of the diagnosis. Yet similar expectoration may occur from simple bronchial hæmorrhages in intense passive congestion of the lungs without infarction. The expectoration in cancer of the lungs may resemble that of pulmonary infarction.

The sudden appearance of pain in the chest, cough, and elevation of temperature, immediately after the hypodermic injection of undissolved preparations of mercury, is attributed to pulmonary embolism. The symptoms disappear in a few days without serious consequences. This complication has been rare in the experience of most of those who have employed this treatment of syphilis, but has led some to abandon the method.

The embolic pneumonias and abscesses caused by infective emboli are pyæmic manifestations, and have been considered in the article on "Pyæmia" in the first volume.

Splenic infarction.—Anæmic infarcts of the spleen, which are commoner than the hæmorrhagic variety, are not usually in the recent state so pale and bloodless as those of the kidney; for the spleen is much richer in blood than the kidney, and in chronic passive congestion, during which the larger number of infarcts occur, the red pulp contains much blood outside of the vessels. Many of these infarcts can be appropriately described as mixed red and white infarcts. Splenic infarcts

vary greatly in size, but in general they are much larger than those occurring under the same conditions in the kidney, as comparatively large arteries in the spleen break up into numerous small terminal twigs. Averaging perhaps two to six centimetres in diameter, a single infarct may occupy one-half or more of the splcen. The recent infarcts are hard, swollen, and more or less wedge-shaped, with the base at the capsule, which is often coated with fibrin; or in older cases is thickened and adherent by fibrous tissue. The great majority are caused by emboli from the left heart or the aorta; but both hæmorrhagic and pale splenic infarcts occur without arterial occlusion; especially in certain acute infective diseases; oftenest in relapsing fever, but also in typhus, enteric fever, cholera, and septicæmia. The causation of the latter is unknown. Ponfick attributes them to venous thrombosis, which may be the cause of the hæmorrhagic infarcts; but it is difficult to understand how it can produce the pale anæmic infarcts. Bland infarcts are mostly absorbed and substituted by pigmentcd, occasionally calcified, scars, which when numerous may cause a lobular deformity of the spleen.

Splenic infarction is often entirely latent. Of the symptoms attributed to it chills and elevation of temperature belong usually to the accompanying acute or chronic endocarditis. Swelling of the spleen, which pertains to chronic passive congestion, is produced also by infarcts. The most diagnostic value attaches to the sudden appearance of pain in the region of the spleen, perhaps increased by lying on the left side, by deep inspiration, and by pressure; and to a perisplenitic friction rub, which can sometimes be detected. These symptoms are not very certain diagnostic points; but when they occur with some manifest source for a splenic embolus, and perhaps with recognised embolism in other organs, they justify a strong suspicion of splenic infarction.

Renal infarction.—There have been a few instances, especially after traumatism, of ncarly total necrosis of a kidney from thrombosis of the renal artery, combined usually with thrombosis of the vein. Usually plugging of the main artery leads to multiple infarction with intervening intact arcas. The capsular arteries suffice for the preservation of at least a narrow outer rim of renal tissue.

Renal infarcts are nearly always anæmic, in the recent state somewhat swollen, and of an opaque pale yellowish colour, with the base of the wedge just beneath the capsule and the apex toward the hilum, most frequently ncar the boundary between the pyramid and cortex. Three zones can oftcn be distinguishcd:—the main central yellowish white mass of necrotic tissuc; next to this a narrow yellow zone of fatty cells, nuclear fragments, and disintcgrating leucocytes; and an outer, irrcgular, variable rim of hyperæmia and hæmorrhage which belongs partly to the infarct and partly to the surrounding tissue. The hæmorrhage may extend a variable distance into the infarct, and in very rare instances genuine hæmorrhagic infarcts occur in the kidney. Numerous scars from old infarcts may produce a form of atrophic kidney to which the epithet embolic is applicable. Thorel finds that a limited regeneration

of the epithelium and even of uriniferous tubules may occur in healing renal infarcts.

Very large infarcts may so stretch the renal capsule as to induce severe pain. In a case diagnosed by Traube an infarct two inches in diameter, projecting well above the surface, caused intense pain and tenderness in the region of the infarcted kidney, with extension of the pain into the corresponding thigh. With the ordinary small infarcts pain is not usually a prominent symptom. The chief sign of diagnostic value is the sudden appearance of blood in the urine in association with disease of the left heart, aortic aneurysm, or other recognised source for a renal embolus. The amount of blood is usually only moderate or evident by microscopical examination of the urine. It is to be remembered that chronic passive congestion of the kidney is itself one of the many causes of hæmaturia.

Infective emboli, which are often capillary in size, cause multiple, often miliary abscesses in the kidney. This is the hæmatogenous variety of acute suppurative nephritis which occurs often in acute infective endocarditis and other forms of pyæmia. Here the pyuria and other renal symptoms are usually of less consequence than those of general infection.

Embolism and Thrombosis of the mesenteric and intestinal arteries.—Thrombosis of the mesenteric veins, which causes lesions and symptoms identical with those following embolism of the mesenteric arteries, has been considered in the preceding article (p. 218). Since Virchow's first description of embolism of the superior mesenteric artery, in 1847, at least seventy cases have been reported of embolism or thrombosis of the mesenteric arteries. The affection, although not common, occurs often enough and is of such gravity as to be of considerable clinical interest. In Watson's collection of cases there are eight which occurred within a single year in Boston. The casuistic literature upon the subject is fairly extensive. The articles of Litten and of Faber contain reports of most of the cases published up to 1875. The principal clinical features were carefully studied by Gerhardt and by Kussmaul in 1863-64. The papers of Watson and of Elliot in 1894-95 refer to about fifty reported cases, of which they have analysed those with satisfactory clinical histories with special reference to surgical treatment. The effects of occlusion of the mesenteric arteries have been experimentally studied by Beckmann, Cohn, Litten, Faber, Welch and Mall, and Tangl and Harley.

The principal conclusions drawn by Mall and myself from our experiments have been stated already in the discussion of the collateral circulation, and of hæmorrhagic infarction following embolism (pp. 239 and 245). It may here be repeated that, according to our experiments, the blood which produces the hæmorrhagic infarction enters by the anastomosing arteries and not by reflux from the veins; that the hæmorrhage cannot be explained by any demonstrable change in the vascular walls, but is the result of retardation and stasis of the circulation and clumping of red corpuscles in the veins and capillaries, attributable in large part

in cases of arterial obstruction to reduction or loss of lateral pulsation of the blood-current; that the ischæmia is increased by the tonic contraction of the intestinal muscle which follows for two or three hours' closure of the superior mesenteric artery; and that the sudden and complete shutting off of the direct arterial supply to a loop of intestine 5 to 10 ctm. in length is followed by hæmorrhage and necrosis of the loop, even when the vessels at each end of the loop are open. These results we obtained by experimentation upon dogs, but there is no reason to suppose that they do not apply to human beings. With the exception of Cohn, the other experimenters explain the infarction by regurgitant flow from the veins and alterations in the vascular walls.

The majority of the cases of hæmorrhagic infarction of the intestine have been due to embolism of the mesenteric arteries, the source of the embolus being usually the left heart, sometimes an atheromatous aorta or aortic aneurysm, and in one instance a thrombus in the pulmonary veins caused by gangrene of the lungs (Virchow). Several cases have been caused by autochthonous thrombosis resulting from arterio-sclerosis, aneurysm, pressure, or the extension of a thrombus from the adjacent aorta. It is probable that a certain number of the cases reported as embolic were referable to primary thrombosis of the mesenteric arteries, as no source for an embolus could be discovered, and the plugs in some of these instances were fresh adherent thrombi. As has been shown in the preceding article, primary thrombi may form in arteries which are free from atheroma or other chronic disease.[1]

In the great majority of the cases the obstruction was in the superior mesenteric artery. The few scattered instances of embolism or thrombosis of the inferior mesenteric artery indicate that this also may, very rarely, cause incomplete hæmorrhagic infarction of the corresponding part of the intestine, but that the collateral circulation here is better, and the lesions likely to consist only in small hæmorrhages in the intestinal mucosa. The inferior mesenteric artery may be obliterated without any manifest disturbance in the structure or function of the part of the intestine supplied by it.

The obstruction may be situated in the main stem or in any of the branches of the superior mesenteric artery. Intestinal infarction has been associated with embolism of the larger branches oftener than with that of the main stem. As the anastomoses through the arterial arches are so free, obstruction of single small branches is without mechanical effects. There have, however, been several instances of intestinal infarction caused by multiple emboli or extensive thrombosis of small branches of the superior mesenteric artery.

[1] Litten has reported two cases of hæmorrhagic infarction of the intestine from thrombosis caused by what he calls "latticed endarteritis" (gitterförmige Endarteriitis) of the mesenteric arteries. So far as I can learn he has not furnished the fuller description which he promised in his article of nine years ago. Without such description there is room for the suspicion that Litten has mistaken the latticework markings sometimes seen after detachment of an adherent thrombus for a special form of endarteritis. It does not appear from his article that he has observed this "latticed endarteritis" except after removing adherent thrombi.

Intestinal infarction is not the imperative result of occlusion of the superior mesenteric artery, as infarction is of occlusion of branches of the splenic and renal arteries, and of the basal cerebral. Both the trunk and the principal branches of this artery may be gradually closed without serious effects. Tiedemann and Virchow have found the superior mesenteric artery completely obliterated by old, firm thrombi or connective tissue without any lesions in the jejunum or ileum. The most remarkable case is that of Chiene, who found in a woman sixty-five years old, with aneurysm of the abdominal aorta, complete obliteration of the cœliac axis and both mesenteric arteries, with an adequate collateral circulation through the greatly distended extra-peritoneal anastomosing arteries. In a number of instances plugging of large branches of the superior mesenteric artery has caused no more than hyperæmia and superficial ecchymoses, without genuine infarction of the intestine.

The rapid and complete closure of the superior mesenteric artery, however, is followed with great regularity, probably constantly, by hæmorrhagic infarction of the intestine. There have been several instances in which embolism or thrombosis of the trunk of this artery has caused hæmorrhagic infarction extending from the lower part of the duodenum into the transverse colon (Oppolzer, Pieper, Faber, Kaufmann), as in the experimental cases. More frequently the infarction is in the lower part of the jejunum and the ileum, corresponding to the occlusion of a principal branch or of several branches supplying this region. The infarction corresponds in general to the area of distribution of the plugged arteries, but it may occupy only a part of this area. In several instances a single small loop or several loops with intervening normal intestine have been infarcted.

As already intimated, the infarction may be complete or only partial. When completely infarcted, the wall of the affected intestine is thickened, œdematous, of a dark red colour from infiltration with blood and covered with lustreless peritoneum. The margins of the infarct are often sharply marked but may pass gradually into the normal bowel. The mucous membrane is necrotic, often defective, and may be coated with a diphtheritic exudate. In a few instances the intestine has been gangrenous over considerable areas, without typical hæmorrhagic infarction, or with the hæmorrhagic appearance adjacent to the gangrene. The lumen of the intestine contains black tarry blood. There is bloody fluid in the peritoneal cavity, and usually a fibrinous, sometimes a fibrino-purulent exudate on the peritoneum covering the infarction; and there may be general peritonitis. The mesentery is succulent and hæmorrhagic, usually in patches, exceptionally in the form of large flat masses of extravasated blood. Areas of fat-necrosis may be present in the mesentery. The mesenteric veins are distended and the mesenteric glands often swollen and hæmorrhagic. Various intestinal bacteria, most commonly the colon bacillus, may make their way into the peritoneal cavity through the necrotic wall. Flexner and I have reported an instance of hæmorrhagic infarction of the jejunum in which

evidences of pneumo-peritonitis, supposed to be due to perforation, existed during life. At the autopsy, made six hours after death, a large amount of gas was found in the peritoneal cavity without perforation. The B. aerogenes capsulatus was present in large numbers in the peritoneal exudate. This case demonstrates the generation of gas in the closed peritoneal cavity. In the intestinal mucosa were gas-blebs which were observed also in one of Faber's cases and in Jürgens' case of intestinal infarction.

The hæmorrhagic infarction is by no means always so completely formed as that just described. There may be no hæmorrhages in the mesentery. The extravasation of blood may be limited to the mucosa, or even to the submucosa, as in one of Ponfick's cases. In an instance of nearly complete thrombosis of the trunk of the superior mesenteric artery, reported by Councilman, there were paralysis, great distension and ecchymoses of the small intestine, but no infarction. Between mere venous hyperæmia with scattered, superficial hæmorrhages, and complete necrosis and infarction, there are all gradations, the controlling factors being doubtless the rapidity and extent of the arterial occlusion and the vigour of the general circulation.

There have been two or three instances in which the anatomical picture of hæmorrhagic infarction of the intestine has been present without discovery of any obstruction in the corresponding arteries or veins. Lycett reports an observation of hæmorrhagic infarction of the small intestine in an infant one month old without discoverable cause.

Hæmorrhagic infarction of the bowel may be insidious in its onset and course; and, in patients profoundly prostrated or with cerebral symptoms, it may occur without the attention of the physician being drawn to any abdominal trouble. Usually, however, the onset is abrupt, and grave intestinal symptoms are present. In the majority of cases, severe colicky pain and abdominal tenderness, either without distinct localisation or most marked near the umbilicus, are prominent and usually the first symptoms. The pain at the beginning is perhaps attributable to the violent, tonic spasm of the intestine which follows sudden occlusion of the superior mesenteric artery. After a few hours this spasm gives place to complete paralysis of the affected part of the bowel, and then the pain may be referable to peritonitis. The local anæmia, hæmorrhage, and necrosis seem, however, quite sufficient to account for the pain. Vomiting, which often becomes bloody and occasionally fæcal, is also usually an early and persistent symptom. By far the most characteristic symptom, which is present in the majority of cases but not in all, is the passage of tarry blood in the stools, which are frequently diarrhœal, and sometimes have the odour of carrion. In nearly all cases there is hæmorrhage into the bowel, but the blood is not always voided. Symptoms of intestinal obstruction—tympanitic distension of the abdomen, fæcal vomiting and obstipation—are in some cases prominent, and are readily explained by the complete paralysis of the infarcted bowel. The subnormal temperature, pallor, cold sweats and collapse,

which appear in most cases, are explicable in part by the intestinal hæmorrhage, and in part by the shock of the destructive lesion. The sensation of a palpable tumour, referable to a collection of blood in the mesentery or to the infarcted bowel, has been noted in only three or four cases.

The chief emphasis for purposes of diagnosis is to be laid upon the occurrence of intestinal hæmorrhage, not explicable by independent disease of the intestine or by portal obstruction, in combination with other symptoms mentioned, and with the recognition of some source for an embolus, perhaps of embolic manifestations elsewhere. In the majority of cases the diagnosis has been intestinal obstruction, or acute peritonitis. The symptoms closely resemble those of intussusception, in which hæmorrhage from the bowel, although generally less abundant than with embolism of the superior mesenteric artery, is common. Fortunately the distinction of hæmorrhagic infarction from intestinal obstruction is not of much practical importance; for if the symptoms and condition of the patient warrant it, an exploratory laparotomy is indicated in both conditions. Elliot, by the successful resection of four feet of infarcted intestine, has brought hæmorrhagic infarction of the intestine into the surgeon's domain.

The prognosis is grave; and with complete infarction and necrosis of the intestine it is almost necessarily fatal, unless surgical relief be available. Watson estimates that in about one-sixth of the cases the location and extent of the infarction are suitable for resection of the bowel. It is impossible to say at present to what extent the prognosis of hæmorrhagic infarction of the intestine is favourably modified by the new possibilities of surgical interference. Gordon has successfully resected two feet of infarcted intestine. This and Elliot's case are the only two in which this operation has been performed; so far as I am aware.

When the infarction is incomplete, and is limited chiefly to the inner coats of the intestine, recovery may doubtless take place. Cohn, Moos, Lereboullet, and Finlayson have reported instances of recovery after symptoms indicative of hæmorrhagic infarction. Packard attributed cicatricial areas found in the mesentery of an old man dead of rupture of the ascending aorta to healed infarction; but no previous history was obtained, and Packard's interpretation does not seem to me to be free from doubt. Death may occur within 20 to 48 hours after the onset, or the duration may be protracted over several days. Karcher has reported the survival of a patient with mitral stenosis for two months after the complete occlusion of the superior mesenteric artery by an embolus, the symptoms being sufficiently characteristic to have permitted a probable diagnosis during life.

Intestinal ulcers due to embolism or thrombosis constitute a distinct class, which has been studied especially by Ponfick, Parenski, and Nothnagel. Parenski relates an instance of operation for intestinal stricture, which at the autopsy was found to be caused by cicatrisation of an ulcer due to embolism of a branch of the superior mesenteric artery. Much

more common are ulcers caused by infective emboli lodging in the small arteries and capillaries in the intestinal wall; they are observed especially in acute ulcerative endocarditis and pyæmia. These emboli cause hæmorrhages, necroses, and miliary abscesses with resulting ulceration. The ulcers are usually multiple, sometimes numerous, and situated in the small intestine and cæcum. The intestinal ulcers occasionally associated with degenerative multiple neuritis are referred by Minkowski and Lorenz to thrombosis caused by disease of the small arteries, which has been repeatedly observed in this form of neuritis.

Embolism and Thrombosis of the thoracic aorta.—Unless there be some abnormal narrowing or obstruction of the aorta, it is hardly possible for an embolus to lodge in this vessel, except at the ostium or the bifurcation. An exception to this rule may result from the detachment of a large aneurysmal clot, which, as in three cases of abdominal aneurysm reported by Bristowe, may block the aorta at or just below the mouth of the aneurysm.

I know of but three instances of embolism of the mouth of the aorta—two reported by Cohn with instantaneous death, and one by Reid in which the patient lived an hour and a half after the first symptoms of partial obstruction.

In a very few instances the lumen of an atheromatous thoracic aorta has been seriously encroached upon, or even obliterated, by thrombotic masses. Such cases have been reported by Trost, Tewat, Carville, Armet, Chvostek, Jaurand, and Pitt. The thrombus may occupy the ascending, the transverse, or the descending aorta, and may occlude the mouths of the left carotid and subclavian arteries. If there remain a sufficient channel for the blood, as in Pitt's case, there is no resulting circulatory disturbance; otherwise there may be paralysis, œdema, gangrene of the lower extremities, and, if the left subclavian is obliterated, of the corresponding upper extremity.

Bochdalek and Lüttich have each described an instance of occlusion of the aorta in infants by the extension of an obliterating thrombus from a dilated ductus Botalli. Far more frequent is stenosis or atresia of the aorta at or near the attachment of this duct, due usually to persistence of the isthmus aortæ, as was first shown by Rokitansky. Of this latter condition about 100 instances have been recorded.

Embolism and Thrombosis of the abdominal aorta.—Graham in 1814 referred to a museum specimen in Glasgow, which had belonged to Allan Burns, of occlusion of the abdominal aorta just above the bifurcation by old laminated coagulum extending into the iliacs. I have found fifty-nine subsequent reports of occlusion of the abdominal aorta by embolism or thrombosis, and have seen references (which I have not consulted) to six or seven other cases.[1] I have not included in this list the detachment of clots from abdominal aneurysms, although Bristowe's three cases

[1] I have not included von Weismayr's case (*Wiener med. Presse*, 1894, p. 1774), as it was reported while the patient was living, and in the discussion some doubt was expressed as to the diagnosis; nor the brief mention made by Teleky, at the same time, of a similar observation.

demonstrate that this may occasion the same symptoms. The monographs and articles of Meynard, Cammarcri, Selter, Rousscl, Charrier and Apert, and Heiligenthal contain references to or reports of forty-seven cases; to these I have added twelve published cases not mentioned by them. The references are at the end of this article.

Three of the patients were living at the time of the reports, and in two fatal cases there was no autopsy. In the remaining fifty-four the plug occupied the lower end of the aorta and extended a variable distance into the arteries below. In thirty-one the plug did not reach higher than the inferior mesenteric artery; in ten the upper extremity lay between the inferior mesenteric and the renals; in three between the renals and the superior mesenteric; in two between the latter and the cœliac axis; in one just below the pillars of the diaphragm, and in seven the length of the plug is not stated. The upper part was often conical; so that, when the plug extended higher than the inferior mesenteric, it was often not obliterating until at or below this artery. In the great majority of cases only the last, or the last two, lumbar arteries were blocked by the thrombus. In several instances a thrombus, either independent or continuous with that in the aorta, occupied the lumbar, the mesenteric, the renal, or other branches of the aorta. In all instances the thrombus extended into the common iliacs, and in many into arteries lower down, sometimes even as far as the posterior tibial, the end being usually lower on one side than on the other.

It is difficult, indeed impossible, from the published descriptions, which are only too often incomplete and unsatisfactory, to determine accurately how many of the cases were referable to embolism and how many to thrombosis. Essentially similar cases have been interpreted differently in this respect by different observers. The plug was usually adherent, and only in relatively few cases were its anatomical characters such (or at least so described) as to indicate positively its nature as embolus or primary thrombus. The majority of cases with sudden or rapid invasion of characteristic symptoms were associated with cardiac disease, or disease of the upper part of the aorta; and would, therefore, naturally be interpreted as embolic. Still in many of these no satisfactory source for a large embolus was demonstrated. Some cases not less abrupt in onset were without any affection of the heart or of the aorta above the plug. The sudden appearance of symptoms of obstruction of the aorta, although strongly indicative of embolism, are not decisive upon this point. Barth, in 1848, described a case of obstruction of the aorta by a cylindrical thrombus extending from the superior mesenteric artery to the bifurcation, and leaving only a narrow channel for the circulation of the blood. There were no circulatory disturbances. If this narrow channel had been suddenly closed at one point, as might readily happen, the symptoms would probably have been those of embolism. It is evident that aortic thromboses secondary to only partly obliterative emboli riding the bifurcation of the aorta, or to emboli or thrombi in the iliacs or lower arteries, may occasion

symptoms like those of primary thrombosis of the aorta. There are several instances of such secondary thrombosis of the aorta in my collection of cases.

Without much confidence in the accuracy of the classification in several instances, I have divided the fifty-nine cases into forty-five referable to embolism of the aorta at the bifurcation, and fourteen due to thrombosis; of the latter, seven were primary, six secondary to embolism of the iliacs, or possibly the femoral, and one to thrombosis of the arteries of the extremities. The source of the aortic embolus is believed to have been the heart in thirty-five cases; aneurysm of the ascending aorta in one; pressure of a tumour on the aorta in two; atheroma of the thoracic aorta in one; in six it was undetermined. The heart was found to be normal at the autopsy in eleven of the fifty-three cases; and in seven both the heart and the aorta above the plug were normal.

Mitral stenosis existed in twenty cases (two of these being caused by thrombi extending from the left auricle into the ventricle), acute mitral endocarditis in three, mitral endocarditis, not further defined, in four, mitral insufficiency without stenosis in one, thrombus in the left auricle without valvular disease in one, thrombi in the left ventricle, mostly without valvular disease, in eight, and large aortic vegetations in one.

The most interesting point in the etiology of plugging of the abdominal aorta, so far as it is permissible to draw conclusions from so few instances, is that nearly thirty-four per cent of the cases were associated with mitral stenosis. In many of these the stenosis was extreme. The question at once arises of the source of the embolus in these cases, for it cannot be supposed that an embolus large enough to occlude the lower end of the aorta could pass through the contracted mitral orifice. Some of the cases may be explained by a smaller embolus caught at the aortic bifurcation, or in an artery lower down, with secondary thrombosis of the aorta; but the sudden onset of motor and sensory paraplegia and of cessation of pulsation in both femoral arteries in a large number of cases seems to demand abrupt stoppage of the circulation through both common iliacs. A few observers who have realised the difficulty here presented have assumed that a large thrombus had formed in the left ventricle and been detached without leaving any trace behind; for only in two or three of the cases with mitral stenosis was there any evidence of a thrombus in the left ventricle or the aorta above the plug. This explanation must be regarded as purely hypothetical. The coexistence in a number of the cases of infarctions of the spleen, kidney, or brain has seemed to some writers strong evidence in favour of the embolic nature of the aortic plug. It is possible that the explanation even of the cases with acute bilateral symptoms referable to aortic obstruction and associated with marked mitral stenosis may be the lodgment of a small embolus followed by thrombosis of the aorta. Although in the classification above given I have placed nearly all the cases with mitral stenosis under embolism, I am nevertheless not disinclined in spite of the rapid onset of the symptoms, and frequently

coexistent infarctions, to interpret many of them as primary thromboses of the aorta. The circulatory conditions with extreme, uncompensated mitral stenosis seem favourable to the occurrence of arterial thrombosis; and, if this view be accepted for the plugging of the abdominal aorta, the question arises whether thrombi frequently present in smaller arteries in association with this form of valvular disease may not oftener be primary than is generally supposed.

In a few cases congenital narrowing of the aorta was noted. In three instances plugging of the abdominal aorta was associated with embolism or thrombosis of arteries of an upper extremity. Coincident thrombosis of the vena cava, iliac, or femoral veins was observed in a few cases. In Jürgens' patient there was hæmorrhagic infarction of the intestine. In several instances hæmorrhages were found at autopsy in the mucous membranes of the bladder and uterus. Herter, in his experiments in my laboratory with ligation of the abdominal aorta in rabbits, found hæmorrhagic infarction of the uterus to be so common a result of this operation that, when it was desired to keep the animals alive for any length of time, we abandoned the use of female rabbits for Stenson's experiment. It does not appear, however, that in human beings hæmorrhage of the uterus is a common sequel of occlusion of the abdominal aorta.[1] It is probable that if search were made in suitable cases in human beings who have died of aortic thrombosis or embolism, the interesting muscular changes described by Herter in the experimental cases would be found; as similar changes had been previously discovered by Litten in an instance of occlusion of the right iliac and femoral arteries. The most important of these muscular alterations are vacuolisation, proliferation of the sarcolemma nuclei, atrophy, and fatty and pseudo-waxy degenerations.

Plugging of the abdominal aorta has occurred most frequently in the course of chronic cardiac or arterial disease; but in some instances it took place during or after an acute infective disease, as acute articular rheumatism, puerperal fever, erysipelas, during convalescence from enteric fever (Forgues), and after pneumonia (Leyden).

Of the fifty-nine cases thirty were females, twenty-seven males, and in two the sex is not stated. Seventeen were between twenty and thirty years of age, twelve between thirty and forty, eight between forty and fifty, thirteen between fifty and sixty, one was nineteen, one sixty-one, and the ages of seven are not given.[2] Marked atheromatous changes in the arteries were noted in fourteen cases. Occlusion of the

[1] It may here be mentioned that Herxheimer, Popoff, and Chiari have each described an instance of hæmorrhagic infarction of the uterus after extensive bilateral plugging of the vessels supplying this organ.

[2] In Lüttich's case already mentioned (p. 273) of thrombosis of the aorta in an infant fourteen days old, a thrombus beginning 4 cm. below the insertion of the ductus Botalli extended into the iliac arteries. Charrier and Apert include in their collection of reports of thrombosis of the abdominal aorta two cases from Alibert's thesis of 1828, one three, and the other three and a half years old, with gangrene of one leg. I have not counted these three cases in my list.

abdominal aorta by embolism or thrombosis, therefore, is not especially a senile affection.

When one considers the manifold conditions under which the abdominal aorta may become partly or completely plugged by embolism or by primary or secondary thrombosis, it is evident that there can be no general uniformity of symptoms. The plug may be so situated as to interfere with the circulation in one leg more than in the other. Diversities arise from variations in the collateral circulation in different cases. Still the majority of patients have presented a well-characterised group of symptoms. In the larger number of cases the onset has been acute, in the minority insidious and gradual. The symptoms have often appeared simultaneously in both legs, but there may be a short or a long interval between the invasion of one and that of the other leg. In the more acute cases the leading symptoms are pain in the legs,—sometimes in the loins and abdomen, sudden or rapidly manifested paraplegia, anæsthesia of the legs, absence of femoral pulsation, and phenomena of mortification extending from the feet upward. In several instances the patients, while walking, have been seized with excruciating pain in the legs, and have fallen paralysed to the ground. The pain is often atrocious and more or less paroxysmal. There may be tenderness on pressure over the occluded aorta. In a few cases pain has not been a prominent symptom.

Although the paraplegia has been repeatedly described as instantaneous in its appearance, it is to be inferred from the histories of carefully observed patients that at least a short interval of time and sometimes several hours and even days elapse before it is complete. In forty-four cases in which there are definite statements about the motor power, there was complete or nearly complete paraplegia in twenty-four; incomplete paralysis of both lower extremities, described in some instances merely as weakness, in ten; paralysis of only one leg in five, and no paralysis in five. The paralysis seems to be usually of the flaccid variety, but in some cases the paralysed muscles are stiff. In Barié's patient the paralysed legs were completely rigid, and it may be inferred that a condition analogous to rigor mortis had set in. With complete paralysis the reflexes and electrical excitability are abolished. Paralysis of the bladder and rectum, with retention of urine and involuntary evacuations, was observed in several cases, but not in the majority.

Of the cases with satisfactory histories in only two was there no disturbance of sensation. In some there was only numbness or some reduction of sensation, but in most there was definite anæsthesia, extending in some instances no higher than the knee,—more frequently to the middle or upper third of the thigh, and in two cases as high as Poupart's ligament. There was sometimes complete analgesia, which, however, did not exclude sensations of spontaneous pain in the legs. In many cases, however, there was hyperalgesia, either in the anæsthetic area or above it.

The symptom of greatest diagnostic value is absence of pulsation in

the arteries of the lower extremities. In three or four instances it was determined that the abdominal aorta below the navel was pulseless. Wilbur observed excessive aortic pulsation above the obstruction. The legs become cold, and their surface temperature may even fall below that of the room (Browne, Manz). Absence of bleeding upon incision and of reactive hyperæmia after application of heat have been noted. The skin, at first pale, soon acquires a livid mottling, and the superficial veins may be dilated. Œdema of one or both legs and cutaneous hæmorrhages are recorded in some of the histories. If the patient lives long enough gangrene usually ensues, and it may be manifest within twenty-seven to forty-eight hours. Gangrene was bilateral in at least twenty-four cases, and unilateral in seventeen. The extent of the gangrene varied greatly in different cases, being sometimes limited to the foot, sometimes reaching the middle of the thigh, and, in Bell's patient, involving the scrotum. Tympanites, diarrhœa, and albuminuria are common. Exceptional symptoms are the appearance of blood in the urine or stools, hæmatemesis, and priapism. Bedsores appeared in many cases, and may appear within a few days from the onset.

Death may occur within twenty-four hours from the beginning of the attack. Fourteen patients died within the first four days, with collapse and rapid, weak, usually irregular pulse. There may be marked improvement in the initial symptoms either in one or in both legs. The larger number of patients die after a variable interval, which may extend over several weeks or even months, from gangrene, decubitus, and sepsis.

Of the deviations from the type may be especially mentioned incomplete manifestation of symptoms on one or both sides, transitory affection of one leg, limitation of the symptoms to one lower extremity only (four cases), and affection of one leg followed after days, weeks, or months by that of the other (six cases). The two cases reported by Barth and by Jean are considered particularly characteristic of slowly forming thrombosis. Here the first symptoms were chiefly numbness and intermittent claudication, which, after a long interval, deepened into paraplegia without gangrene.

All but three cases terminated fatally, more frequently from the remote effects than from the immediate shock of occlusion of the aorta. The three instances of survival with marked amelioration of all the symptoms are reported by Gull, Chvostek, and Nunez. These cases began acutely with severe pains, paraplegia, disturbances of sensation, coldness and lividity of the lower extremities. The femoral pulse disappeared completely in Gull's and in Nunez's cases, but in Chvostek's it could still be felt, although it was feeble. In Chvostek's patient patches of superficial gangrene appeared; but in the other two cases there was no gangrene. Nunez reports that after a year and a half there was no return of the femoral pulse on either side.

Since the demonstration by Schiffer and Weil, confirmed by Ehrlich and Brieger, Spronck, Herter, and others, that the paraplegia which

follows immediately or very shortly after ligation of the abdominal aorta just below the renal arteries in rabbits (Stenson's experiment) is due to ischæmia of the lumbar cord, many have assumed that the same explanation applies to the paraplegia in human beings after occlusion of the abdominal aorta. If the rabbit's aorta be tied for an hour, and the ligature be then removed, the paraplegia and paralysis of the bladder and rectum are permanent, the gray matter of the lumbar cord undergoes necrosis, and a genuine myelitis affecting chiefly the gray but also the white matter ensues. The same experiment gives negative results with the cat and usually with the dog. In view of the great interest of the subject, it is, to say the least, remarkable how few of the reports of autopsies on persons dead of embolism or thrombosis of the aorta have anything to say about the condition of the spinal cord. Roussel and Heiligenthal observed no macroscopic changes in the spinal cord. In Bell's and Barié and du Castel's cases the cord was microscopically normal, save congestion in the latter. Broca, Legroux, and Malbranc noted with the naked eye changes in colour, from which no definite conclusions can be drawn. The only detailed report of a microscopical examination of the cord is that of Helbing, who found, in the lumbar region of a man who lived thirty-nine days after embolism of the abdominal aorta, degeneration of the anterior and posterior nerve-roots, more marked on one side than the other; and degenerations in the cord for the most part explicable by the changes in the nerve-roots. The lesions of the cord were quite unlike those found in experimental cases, and are interpreted by Helbing as essentially analogous to those after amputation, and not referable to ischæmia of the cord.

As the matter now stands, there are no direct observations to support the opinion that the paraplegia following embolism or thrombosis of the abdominal aorta in human beings is caused by ischæmia of the cord, so that the old explanation which refers it to ischæmia of the peripheral nerves and muscles has the most in its favour. The question of the possibility of this mode of production of paraplegia, however, seems to me still open, and it is to be hoped that hereafter fatal cases of this rare condition will not be reported without satisfactory microscopical examination of the spinal cord. The anatomical investigations of Kadyi and of Williamson at least do not exclude the possibility that the lumbar cord in human beings is dependent to a considerable extent for its blood-supply upon the lumbar arteries.

The diagnosis of ischæmic paraplegia from spinal paraplegia can generally be made without difficulty by the absence of femoral pulsation, by the coldness and lividity of the extremities, and by the occurrence of gangrene in the former.

Embolism of arteries of the extremities.—Of the arteries of the extremities the popliteal and the femoral are the most frequent recipients of emboli. The results of embolism of arteries supplying the extremities are essentially similar to those of arterial thrombosis, which have already been considered (p. 206). The modifications resulting from the sudden

advent of embolism are sufficiently self-evident. There may be severe pain at the moment of impaction and at the site of lodgment of the embolus. The general principles involved in the differentiation of embolism from thrombosis have been presented under Diagnosis (p. 253).

Hepatic infarction.—As the effects of infective emboli in branches of the portal vein and of the hepatic artery have been considered elsewhere in this work (vol. i. p. 601, and vol. v. p. 123), only the possible mechanical effects of hepatic emboli require consideration here. Although the intrahepatic branches of the hepatic artery and of the portal vein are terminal vessels, their capillary communications are so abundant that, as a rule, embolism or thrombosis of the hepatic vessels causes no interference with the circulation in the liver. Experiments of Cohnheim and Litten and of Doyon and Dufourt have demonstrated that complete interruption of the circulation through the hepatic arteries of the rabbit and the dog is followed by necrosis of the liver. Chiari has observed an instance of necrosis of the entire liver caused by closure of the trunk of the hepatic artery beyond the origin of the pyloric branch.

In rare instances, and under circumstances at present not thoroughly understood, a condition somewhat resembling hæmorrhagic infarction may follow plugging, either by an embolus or a thrombus, of branches of the portal vein. Instances of this occurrence in human beings have been reported by Osler, Rattone, Klebs, Lubarsch, Köhler, Pitt, Zahn, and Chiari; the last-named having seen 17 cases, of which 15 were embolic. A somewhat similar condition was observed by Arnold after retrograde embolism of the hepatic vein. Pale wedge-shaped areas have been observed, but in most of the cases there were circumscribed dark red or reddish-brown wedge-shaped, rectangular or irregular areas.

Köhler and Chiari found that the red colour is due mainly to dilatation of the intralobular capillaries, with atrophy of the liver-cells. Genuine coagulative necrosis is not present. The affected areas are patches of circumscribed red atrophy rather than typical hæmorrhagic infarcts. Zahn observed the same condition in a human liver after plugging of portal branches, and reproduced it experimentally by emboli of sterilised mercury injected into mesenteric veins. In his experimental cases the change in the liver did not begin until the eighth day, and was distinct after thirty-five days. It is probable that the areas do not undergo cicatrisation.

Rattone's theory, based upon experiments, that occlusion of branches of both the hepatic artery and portal vein is essential for the production of infarction of the liver, is not supported by the observations in human beings. Klebs, whose two cases followed injury of the liver, as was true also of Lubarsch's observation, attributes the infarction to extensive capillary thrombosis. Köhler considers that the essential factor is combination of occlusion of branches of the portal vein with obstruction to the return flow from the hepatic veins. Chiari believes that the second factor, to be added to the plugging of portal branches, is feeble flow through the hepatic artery, from weakness of the general

circulation. Wooldridge, by injecting coagulative tissue-extracts into the jugular vein of the dog, caused extensive clotting of blood in the portal vein and its branches, followed by numerous hæmorrhages and necroses in the liver; but the interpretation of these results as actual infarctions does not seem to me certain, inasmuch as these extracts in toxic doses produce a hæmorrhagic diathesis, and may cause necroses in various situations independently of thrombosis. The focal necroses so often met with in the liver in various infective and toxic states do not usually stand in any definite relation to closure of the vessels (Welch and Flexner).

Embolism of the coronary arteries of the heart.—This is far less frequent than thrombosis, but Marie's position, that scarcely more than one or two of the reported cases of coronary embolism are free from all criticism, seems to me too extreme. Metastatic abscesses in the heart are not particularly rare manifestations of pyæmia. To what extent they are caused by coarse infective emboli, or by the lodgment of isolated bacteria, or small bacterial clumps, does not appear to be established. The heart ranks next to the kidney as the most frequent seat of abscesses following intravascular injection of the pyogenetic staphylococci in rabbits.

Virchow, Chiari, Rolleston, Hektoen, and others have published observations of bland embolism of the coronary arteries. I have observed an instance in which the embolic nature of the plug seemed to me conclusively established. A woman, 36 years old, who had presented symptoms of mitral insufficiency, died suddenly after a paroxysm of dyspnœa and precordial distress lasting two or three minutes. I found an entirely loose grayish plug, 4 mm. long, with a rough irregular extremity, completely occluding the descending branch of the left coronary artery near its origin. There was no atheroma at the site of lodgment of the embolus, although there were a few patches in other parts of the coronary arteries. The segments of the mitral valve were thickened, retracted, and beset with both old and fresh vegetations, and globular thrombi were present in the left auricular appendix. There were also fresh vegetations upon the aortic valve. There were infarcts in the spleen and kidneys. There were no fibroid patches or infarction in the myocardium.

The effects of embolism of the coronary arteries are like those of thrombosis, which have already been considered (p. 208).

Embolism and Thrombosis of the retinal vessels.—Plugging of the retinal vessels is of general pathological as well as special ophthalmological interest, for it is possible to observe with the ophthalmoscope the circulatory disturbances in the retina. Ischæmia and stasis follow immediately closure of the central artery of the retina by an embolus. Vision is lost with characteristic suddenness. Both the arteries and the veins are narrowed, the latter being often unequally contracted. Subsequently the veins may dilate to some extent, especially in the periphery of the retina, and present ampulliform swellings. An interesting phenomenon is the appearance in the veins of an intermittent, sluggish

stream of broken cylinders of red corpuscles, separated by clear spaces; and by pressure on the eye-ball a similarly interrupted current may often be made to flow through arteries and veins. This appearance of interrupted columns of blood is evidently similar to that observed by Mall and myself after closure of the superior mesenteric artery and previously described (p. 245). After a short time the optic papilla becomes pale and gray, and the retina, especially in the neighbourhood of the papilla and macula, assumes an opaque, grayish white, œdematous aspect. Hæmorrhages are exceptional. A characteristic ophthalmoscopic appearance is the cherry-red spot in the centre of the macula, caused by the red colour of the choroid shining through. There may be more or less return of the circulation with improvement and even complete restoration of vision; but the prognosis as regards sight is in general unfavourable, as atrophy of the retina and of the optic nerve is likely to ensue. The prognosis is more favourable with embolism of branches of the retinal artery. Here multiple hæmorrhages usually occur.

Thrombosis of the central retinal vein is distinguished from plugging of the artery especially by the abundant hæmorrhages. With occlusion of the central artery the condition is anæmic infarction, and with plugging of the vein hæmorrhagic infaretion.

There is some difference of opinion as to the relative frequency of embolism and of thrombosis of the central retinal artery. Of 129 cases collected by Fischer, ninety-one had heart disease; whereas Kern reports that of twelve cases in Haab's clinic only two had demonstrable cardiac disease; and of eighty-three cases, collected from the records, in 66 per cent there was no demonstrable source for an embolus. The latter author, therefore, regards the majority of plugs in the central artery of the retina as primary thrombi. The generally accepted opinion, however, is that embolism is more common than thrombosis of the retinal arteries.

Treatment.—In the preceding pages mention has been made of the surgical treatment of hæmorrhagic infarction of the intestine and of gangrene of the extremities; and under "Thrombosis" the importance of preventing so far as may be the separation of emboli has been emphasised. The general indications in the treatment of embolism are essentially similar to those already considered for thrombosis (p. 233).

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